Synthesis, Resolution, and Preliminary Evaluation of *trans*-2-Amino-6(5)-hydroxy-1-phenyl-2,3-dihydro-1*H*-indenes and Related Derivatives as Dopamine Receptors Ligands

Francesco Claudi,*[,†] Gian Mario Cingolani,[†] Antonio Di Stefano,[†] Gianfabio Giorgioni,[†] Francesco Amenta,[‡] Paolo Barili,[‡] Francesca Ferrari,[§] and Daniela Giuliani[§]

Dipartimento di Scienze Chimiche, Università di Camerino, Via S. Agostino 1, 62032 Camerino (MC), Italy, Sezione di Anatomia Umana, Università di Camerino, Via Scalzino 3, 62032 Camerino (MC), Italy, and Istituto di Farmacologia, Università di Modena, 41100 Modena, Italy

Received April 29, 1996[⊗]

The present work reports the synthesis of enantiomeric pairs of the *trans*-2-amino-6-hydroxy-1-phenyl-2,3-dihydro-1*H*-indene [(+)-**14a**, (−)-**14a**] and *trans*-2-amino-5-hydroxy-1-phenyl-2,3-dihydro-1*H*-indene [(+)-**14b**, (−)-**14b**] and their *N*,*N*-di-*n*-propyl [(+)- and (−)-**15a,b**], *N*-methyl-*N*-allyl [(+)- and (−)-**16a,b**], and *N*-methyl-*N*-*n*-propyl [(+) and (−)-**17a,b**] derivatives obtained by a combination of stereospecific reactions and optical resolution. The new compounds were evaluated for their affinity at the dopamine D_1 and D_2 receptors. The amines (+)- and (−)-**14a**, incorporating the D_1 pharmacophore 2-phenyl-2-(3-hydroxyphenyl)ethylamine in a *trans* extended conformation, and their derivatives displayed D_1 and D_2 affinity in the nanomolar range. On the other hand, the enantiomers (+)- and (−)-**14b**, (+)- and (−)-**15b** displayed high affinity and selectvity for the D_1 receptor. In a preliminary behavioral study on rats (+)-**14b**, and to a greater extent (+)-**15b**, promoted episodes of intense grooming, thus indicating that they act as central D_1 agonists. The *trans*-2-amino-5-hydroxy-1-phenyl-2,3-dihydro-1*H*-indenes (+)-**14b** and (+)-**15b** represent selective D_1 agonists lacking a catechol group, which should meet the prerequisites for a central nervous system penetration.

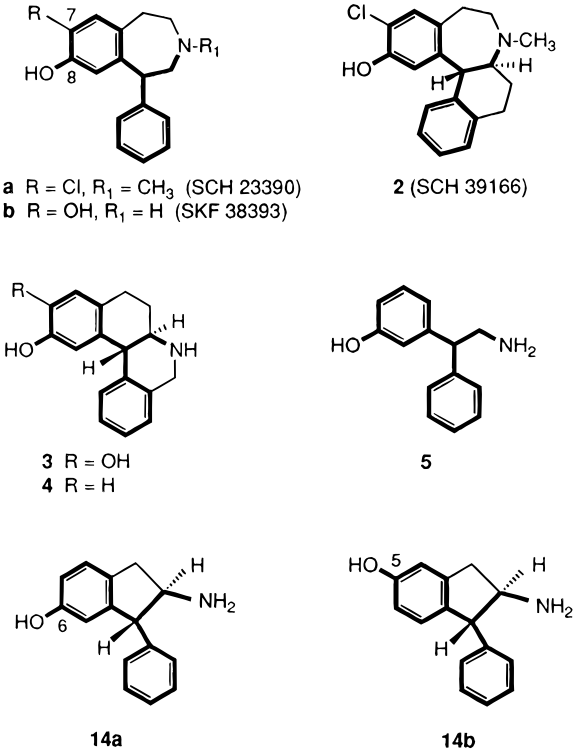
Introduction

The physiological effects of the neurotransmitter dopamine (DA) are mediated by receptors, the dysfunction of which is implicated in psychiatric, neurological, and neuroendocrine disorders such as schizophrenia, Parkinson's disease, and hyperprolactinemia. At present, the classification commonly accepted divides DA receptors into two families: D_{1-like} and D_{2-like}. The D_{1-like} family includes the D_1 and D_5 receptors, whereas the D_2, D_3, and D_4 receptors belong to the D_{2-like} family.[1]

While many researches were addressed on the discovery of new selective therapeutic agents acting on D_{2-like} receptors, the development of selective agonists or antagonists for D_{1-like} receptors has received less attention. The discovery by Schering-Plough Research of the (*R*)-(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (**1a**, SCH 23390, Chart 1) and the introduction of its tritiated derivative as radioligand have facilitated research on the function of D_{1-like} receptors in the central nervous system. Compound **1a** is the first selective D_{1-like} receptor antagonist and the prototype of the 1-phenyl-3-benzazepine class which includes both agonists and antagonists.[2] The specific D_{1-like} antagonist, (−)-*trans*-11-chloro-6,6a,7,8,9,13b-hexahydro-7-methyl-5*H*-benzo[*d*]naphtho[2,1-*b*]azepin-12-ol (**2**, SCH 39166)[3] has been proposed subsequently as a potential antipsychotic drug for the treatment of schizophrenia without acute extrapyramidal side effects (EPS).[4]

Dopaminergic 1-phenyl-3-benzazepines display a high degree of enantioselectivity, and the activity resides only in an enantiomer as observed also in **2**. This compound can exist as *cis* and *trans* isomers and contains two chiral carbons. In binding studies, the *trans* isomer showed D_{1-like} affinity higher than that of the *cis* isomer. Among the enantiomers of **2**, the compound with a 6aS,-13bR configuration showed high affinity for the D_{1-like} receptors. A similar situation was observed in the hexahydrobenzo[*a*]phenanthridine class in which only the *trans* isomer **3** with a 6a*R*,12b*S* configuration has

Chart 1



1a R = Cl, R_1 = CH_3 (SCH 23390)
1b R = OH, R_1 = H (SKF 38393)

2 (SCH 39166)

3 R = OH
4 R = H

5

14a

14b

† Dipartimento di Scienze Chimiche, Università di Camerino.
‡ Sezione di Anatomia Umana, Istituto di Farmacologia, Università di Camerino.
§ Istituto di Farmacologia, Università di Modena.
⊗ Abstract published in *Advance ACS Abstracts,* September 1, 1996.

S0022-2623(96)00318-4 CCC: $12.00

high affinity for D_{1-like} receptors.[5] In both classes, the presence of a catechol function induces agonistic activity (**1b**[6] and **3**), while a single hydroxyl group at a position meta to the ethylamine chain is a prerequisite for D_{1-like} binding and antagonistic activity (**1a**, **2,** and **4**).[7]

Nichols and Brewster have proposed a conformational model for the D_1 receptor, suggesting that the hydroxyphenylethylamine moiety embedded in the hexahydrobenzo[*a*]phenanthridines **3** and **4** should be in a *trans* extended conformation.[5] This structural feature is probably an important contributor to the D_{1-like} selectivity. The unsubstituted phenyl ring seems to be responsible for the induction of D_{1-like} selectivity as well as for an increased affinity and potency by interacting with an accessory binding region of the receptor.[8] On the basis of the structure of cloned catecholaminergic G protein receptors,[1] the same receptor model postulates that an aspartate residue binds the protonated amino group and that the hydroxyls of two serine residues bind the catechol function.[8,9]

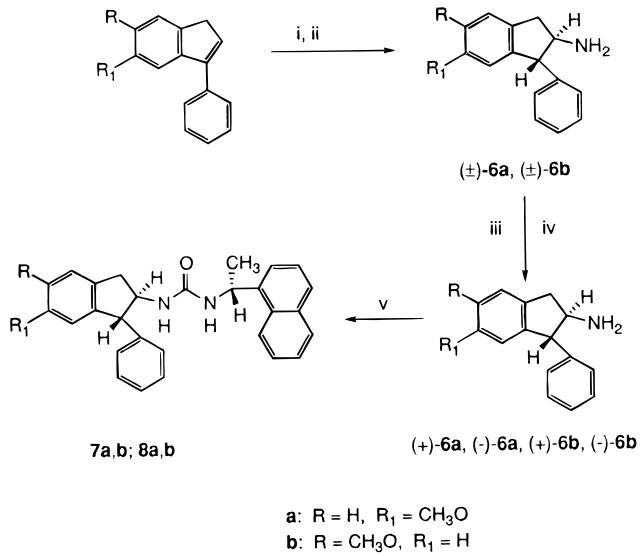
On the basis of these findings, we have synthesized the enantiomers of *trans* -2-amino-6-hydroxy-1-phenyl-2,3-dihydro-1*H*-indene ((+)- and (−)-**14a**, Chart 1), which contain the putative pharmacophore of D_{1-like} receptor, the 2-phenyl-2-(3-hydroxyphenyl)ethylamine **5** with a *trans* conformation.[5] Compound **14a** contains an amino group *trans* to the 1-phenyl ring and two asymmetric centers (C1 and C2) and produces two enantiomers.

The structure−activity relationships (SAR) on 1-phenyl-3-benzazepines indicate that the 8-hydroxy group is a critical pharmacophoric element, but the conceptual model of the D_{1-like} receptor proposes that also the 7-hydroxy group interacts with a serine residue and is determinant for the D_{1-like} agonistic activity.[8] In view of this, we also synthesized the enantiomers of *trans*-2-amino-5-hydroxy-1-phenyl-2,3-dihydro-1*H*-indene ((+)- and (−)-**14b**). In both compounds, **14a** and **14b**, the amino group was substituted with methyl, allyl, and n-propyl groups which, as a rule, affect the affinity for DA receptors.[10a,b]

Chemistry

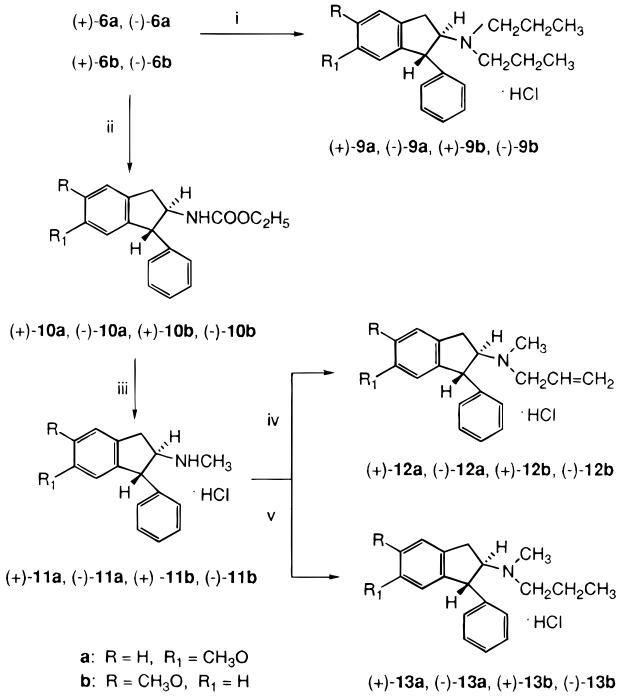
The new compounds were synthesized from 5- or 6-methoxy-3-phenyl-1*H*-indene prepared by reaction of 6- or 5-methoxyindan-1-one with phenylmagnesium bromide according to the procedure reported in the literature for 3-phenyl-1*H*-indene[11] (Scheme 1). The methoxy-3-phenyl-1*H*-indenes were converted to *trans*-2-amino-6(5)-methoxy-1-phenyl-2,3-dihydro-1*H*-indenes (±)-**6a** and (±)-**6b** by a stereospecific hydroboration and reaction of organoboranes with hydroxylamine *O*-sulfonic acid.[12] The *trans* configuration of (±)-**6a** and (±)-**6b** was established on the *cis* addition mechanism of the diborane and the ^{1}H-NMR data. In the NMR spectra of the two compounds, we noted a coupling constant of 7.93 Hz for the hydrogens at the 1- and 2-positions. This value is very similar to that reported in literature (8 Hz) for the same hydrogens in *trans*-2-amino-1-phenyl-2,3-dihydro-1*H*-indene.[13] The resolution of the enantiomers of (±)-**6a** and (±)-**6b** was accomplished by recrystallization of the (+)- and (−)-L-dibenzoyltartaric acid salts. The free bases were obtained by treatment of the salts with aqueous ammonia. The enantiomeric excess was determined derivatizing

Scheme 1[a]



[a] (i) $NaBH_4$, BF_3; (ii) NH_2OSO_3H; (iii) (−)-dibenzoyl-L-tartaric acid; (iv) (+)-dibenzoyl-L-tartaric acid; (v) (*R*)-(−)-1-(1-naphthyl)-ethyl isocyanate.

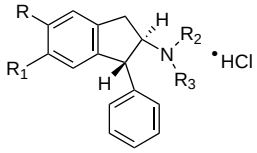
Scheme 2[a]



[a] (i) Propionic acid, $NaBH_4$, HCl; (ii) ethyl chloroformate, triethylamine; (iii) $LiAlH_4$, HCl; (iv) allyl bromide, K_2CO_3, HCl; (v) *n*-propyl iodide, K_2CO_3, HCl.

the amines with (*R*)-1-(1-naphthyl)ethyl isocyanate.[14] The inspection and integration of the benzylic and methyl protons signals in the diastereomeric ureas **7** and **8** provided an enantiomeric excess greater than 98%. The di-*n*-propyl derivatives **9** were obtained by alkylation of the enantiomeric free bases **6a,b** with the $NaBH_4$−propionic acid complex.[15] The *N*-*n*-propyl-*N*-methyl and *N*-allyl-*N*-methyl derivatives were prepared as outlined in Scheme 2. Cleavage of the methoxyl groups was achieved by employing the gentle methionine−methanesulfonic acid procedure.[16] The hydroxy derivatives **14a,b**−**17a,b** are listed in Table 1.

Table 1. Affinities of *trans*-2-Amino-6-hydroxy-1-phenyl-2,3-dihydro-1*H*-indenes and *trans*-2-Amino-5-hydroxy-1-phenyl-2,3-dihydro-1*H*-indenes at Striatal Dopamine Receptors[a]



					K_i (nM)	
compd	R	R_1	R_2	R_3	D_1	D_2
(+)-**14a**	H	OH	H	H	2.5 ± 0.2	0.59 ± 0.06
(−)-**14a**	H	OH	H	H	34.5 ± 2.4	0.89 ± 0.07
(+)-**15a**	H	OH	$(CH_2)_2CH_3$	$(CH_2)_2CH_3$	28.5 ± 1.6	51.5 ± 2.3
(−)-**15a**	H	OH	$(CH_2)_2CH_3$	$(CH_2)_2CH_3$	26.4 ± 2.5	0.84 ± 0.06
(+)-**16a**	H	OH	CH_3	CH_2CHCH_2	3.0 ± 0.3	37.5 ± 1.4
(−)-**16a**	H	OH	CH_3	CH_2CHCH_2	0.79 ± 0.09	0.43 ± 0.03
(+)-**17a**	H	OH	CH_3	$(CH_2)_2CH_3$	0.90 ± 0.08	0.30 ± 0.03
(−)-**17a**	H	OH	CH_3	$(CH_2)_2CH_3$	0.88 ± 0.09	0.34 ± 0.02
(+)-**14b**	OH	H	H	H	1.87 ± 0.06	>1000
(−)-**14b**	OH	H	H	H	18.7 ± 0.8	>1000
(+)-**15b**	OH	H	$(CH_2)_2CH_3$	$(CH_2)_2CH_3$	1.4 ± 0.1	>1000
(−)-**15b**	OH	H	$(CH_2)_2CH_3$	$(CH_2)_2CH_3$	1.76 ± 0.07	>1000
(+)-**16b**	OH	H	CH_3	CH_2CHCH_2	>1000	>1000
(−)-**16b**	OH	H	CH_3	CH_2CHCH_2	>1000	>1000
(+)-**17b**	OH	H	CH_3	$(CH_2)_2CH_3$	>1000	>1000
(−)-**17b**	OH	H	CH_3	$(CH_2)_2CH_3$	>1000	>1000
18	OH	OH	H	H	5.5 ± 0.1	>1000
DA					>1000	>1000
(*R*)-(+)-SCH 23390					0.73 ± 0.05	>1000
PPHT					>1000	2.70 ± 0.12

[a] Binding studies were performed using frozen sections of rat neostriatum with [^{3}H]SCH 23390 (D_1 selective antagonist) and [^{3}H]spiperone (D_2 selective antagonist) as radioligands. K_i represents the inhibition constant which was calculated according to Cheng and Prusoff. Values are the means ± SEM of five to seven independent triplicate experiments.

Biological Results and Discussion

The target compounds were screened for their *in vitro* binding affinity to DA receptors, using sections of rat neostriatum according to the technique previously described.[17] Rat neostriatum expresses primarily D_1 and D_2 subtypes.[18] The radioligands [^{3}H]SCH 23390 (D_1 selective) and [^{3}H]spiperone (D_2 selective) were used, while the reference compounds used were (*R*)-(+)-SCH 23390 (a selective D_1 antagonist), (±)-2-(*N*-(phenylethyl)-*N*-propylamino)-5-hydroxytetralin hydrochloride (PPHT, a selective D_2 agonist), and DA (Table 1).

Data obtained for 2-amino-6-hydroxy-1-phenyl-1*H*-indenes (+)- and (−)-**14a**−**17a**, which hold the pharmacophore 2-phenyl-2-(3-hydroxyphenyl)ethylamine in a *trans* conformation, indicate that these compounds interact with both DA receptor subtypes. The primary amines (+)-**14a**, (−)-**14a** show higher affinity for the D_2 than for the D_1 receptor, and (−)-**14a** is 38 times more selective for the D_2 receptor. Introduction of two alkyl substituents on the amino group influences in a different way the affinity for D_1 and D_2 receptors. Dipropylation of (+)-**14a** decreases D_1 and D_2 affinity, while the same substitution on (−)-**14a** does not affect D_1 and D_2 affinity. The introduction of a methyl and an allyl group on (+)-**14a** decreases only D_2 affinity, and (+)-**16a** is selective for D_1 receptor (12 times), while the same substitution on (−)-**14a** increases only D_1 affinity. Methyl and propyl introduction on the amino group increases D_1 affinity, providing compounds [(+)-**17a** and (−)-**17a**] with high affinity for both receptors. Thus, the reduction of alkyl group dimensions (from propyl to methyl) increases D_1 affinity. Moreover, different affinities were observed for (+)- and (−)-**14a** at D_1 receptor, for (+)- and (−)-**15a** at D_2 receptor, and for (+)- and (−)-**16a** at D_1 and D_2 receptors.

These results indicate that the compounds (+)- and (−)-**14a**−**17a** are not highly selective, displaying D_1 and D_2 affinity. This suggests that the 2-phenyl-2-(3-hydroxyphenyl)ethylamine pharmacophore embedded in these compounds in a *trans* conformation does not induce high D_1 selectivity. This finding could be explained on the basis of the structural differences among our compounds, having an exocyclic amino group, and tetrahydrobenzazepines or hexahydrophenanthridines, which hold the pharmacophore in a more rigid framework. Conformational analysis and SAR in the benzazepines series suggest that the biologically active conformation of the tetrahydrobenzazepine ring is a chair conformation with an equatorial phenyl ring.[19] In contrast, an axial phenyl ring is detrimental to D_1 receptor affinity.[3] In an interesting study on the SAR of the benzo[*a*]phenanthridines **3** and **4**, Brewster et al. concluded that the unsubstituted phenyl ring attached at the 2-position of the ethylamine side chain is nearly coplanar with the catechol ring.[20]

In the *trans*-2-amino-6-hydroxy-1-phenyl-2,3-dihydro-1*H*-indenes (+)- and (−)-**14a**−**17a**, the unsubstituted phenyl ring and the amino group are not rigidly constrained, and a free rotation is allowed. Thus, the orientation of the two groups can deviate from that preferred by the D_1 receptor and the two phenyl ring may be not coplanar. A similar situation could be responsible for the moderate affinity observed in *trans*-1-phenyl-2-amino-6,7-dihydroxytetralin for both D_1 and D_2 receptors.[20] Moreover, on the basis of current models, the D_1 receptor requires the catechol function for high affinity, while the D_2 receptor is much less demanding, and only a single hydroxy group is necessary to confer affinity.[5,20−22] Thus, these considerations

could explain the low selectivity of the monophenolic compounds (+)- and (−)-**14a**−**17a** for D_1 and D_2 receptors.

An unexpected result was obtained with the *trans*-2-amino-5-hydroxy-1-phenyl-2,3-dihydro-1*H*-indenes. In this series, the primary amines (+)-**14b**, (−)-**14b**, and the *N*,*N*-di-*n*-propyl derivatives (+)-**15b** and (−)-**15b** demonstrate high affinity and selectivity for D_1 receptor. It is noteworthy that the enantiomers **14b** bind streoselectively to D_1 receptor; (+)-**14b** (K_i = 1.87 nM) is 10 times more potent than (−)-**14b** (K_i = 18.68 nM). The *N*,*N*-di-*n*-propyl derivatives show the same affinity for D_1 receptor, while the *N*-methyl-*N*-allyl and *N*-methyl-*N*-propyl derivatives (+)- and (−)-**16b**,**17b** are inactive at both receptor subtypes. It is of interest to note that in both series the N-alkylation with methyl and allyl or methyl and propyl groups greatly affects the D_1 affinity; this increases in the 6-OH derivatives [(−)-**16a**, (+)-**17a,** and (−)-**17a**] and decreases in the 5-OH derivatives [(+)-**16b**, (−)-**16b**, (+)-**17b**, and (−)-**17b**].

The structure of our compounds suggests that they can interact with the two primary binding sites of D_1 and D_2 receptors, namely an aspartate residue (amino group) and a serine residue (OH group). From the Dreiding model of 2-amino-5-hydroxy- and 2-amino-6-hydroxy-1-phenyl-2,3-dihydro-1*H*-indene it appears that the distances between 5-OH or 6-OH and the nitrogen are quite similar. Therefore it is possible to hypothesize that the two hydroxyls bind at the same serine residue and, as a consequence, the arrangement of the unsubstituted phenyl ring could be different for the two series of compounds. Moreover, it seems that also the steric hindrance of the substituents on the amino group affects the binding. In the 6-OH indenes (+)- and (−)-**14a**−**17a**, showing D_1 and D_2 affinity, it may be hypothesized that the unsubstituted phenyl ring cannot properly fit the phenyl accessory binding site.[8] The size of the substituents influences the D_1 affinity that increases when a propyl is replaced by a methyl group. On the other hand, for the 5-OH indenes the phenyl ring arrangement seems to be optimal for D_1 interaction only in compounds (+)- and (−)-**14b**,**15b**, and D_1 affinity disappears when the *N*,*N*-di-*n*-propylamino group is replaced by a *N*-allyl-*N*-methylamino or *N*-methyl-*N*-*n*-propylamino group. From this work it appears that the size of the substituents on the amino group greatly affects the affinity at DA receptors.

A previous study showed that the *trans*-2-amino-5,6-dihydroxy-1-phenyl-2,3-dihydro-1*H*-indene (**18**, Table 1) does not displays affinity for DA receptors.[23] Since these results were not consistent with our data on 5-OH or 6-OH indenes, compound **18** as been resynthesized and tested with the same binding assay technique. Results obtained indicate that **18** binds selectively the D_1 receptor with a K_i of 5.5 nM and did not display D_2 receptor affinity. Binding experiments with this compound were made difficult to its extreme photosensitivity in aqueous solution. Hence, all procedures were done in a dark room. On the contrary our compounds, containing a phenol instead of a catechol group, are highly stable in solution.

To further establish the pharmacological profile, attempting to gain information about their possible central agonist or antagonist activity, the compounds (+)-**14b** and (+)-**15b** (D_1 selective) were tested *in vivo* with behavioral methods. It is well-known that D_1 agonists induce prominent grooming in the rat, while pretreatment with D_1 antagonists reduces the grooming.[24,25] The intraperitoneal administration of (+)-**15b** (1.5−30 μmol/kg) to rats significantly increased grooming, which was rather sporadic in vehicle-treated animals accustomed to the new cage (Figure 1). The effect was maximal at 3 μmol/kg and disappeared completely at the dose of 30 μmol/kg. Pretreatment with the DA D_1 antagonist (*R*)-(+)-SCH 23390 (1.8 μmol/kg) significantly counteracted the grooming response induced by 3 μmol/kg of (+)-**15b**. The D_1 agonist (*R*)-(+)-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (**1b**, SK&F 38393), comparatively tested at 3 and 30 μmol/kg, enhanced grooming, and also in this case, the phenomenon was antagonized by (*R*)-(+)-SCH 23390 at 1.8 μmol/kg. Figure 2 shows that also (+)-**14b** (2−40 μmol/kg) significantly increased grooming at 4 μmol/kg with respect to vehicle, and the D_1 antagonist (*R*)-(+)-SCH 23390 inhibited the grooming stimulation. However (+)-**14b** seems to be *in vivo* less active than (+)-**15b**. At all doses tested, (+)-**14b**, (+)-**15b**, and (*R*)-(+)-SK&F 38393 failed to induce other typical DA D_2 agonist responses[26] such as stereotyped behavior, stretching−yawning, and penile erection (data not shown). Thus, the behavioral response to (+)-**14b** and (+)-**15b** was induction of grooming that is characteristic of all preferential and selective D_1 receptor agonists examined to date.[24,27] These preliminary studies also indicate that (+)-**14b** and (+)-**15b** cross blood−brain barrier and are active on central D_1 receptors.

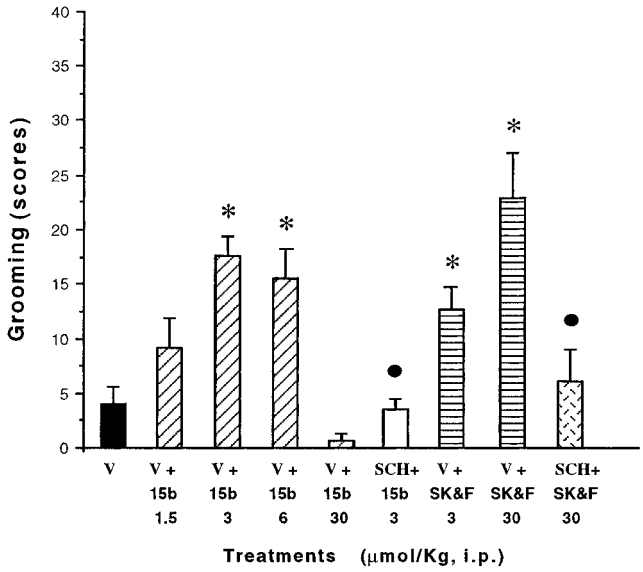


Figure 1. Effect of (*R*)-(+)-SCH 23390 on (+)-**15b** and (*R*)-(+)-SK&F 38393-induced grooming in rats. Vehicle [V, physiological (0.9%) saline], (+)-**15b**, and (*R*)-(+)-SK&F 38393 (SK&F) were intraperitoneally (ip) injected 5 min before the test (30 min); V and (*R*)-(+)-SCH 23390 (SCH) at 1.8 μmol/kg were ip injected 25 min before V, (+)-**15b**, and SK&F. Histograms are the means ± SEM of the scores for grooming for each treatment group (at least eight animals). An asterisk (*) shows results significantly different from those for vehicle-treated animals; a dot (●) indicates results significantly different from those of respective controls (Kruskal Wallis test followed by Mann Whitney *U* test).

In preliminary behavioral studies, the derivatives (−)-**15a** and (−)-**16a**, which displayed affinity for D_1 and D_2 receptors, did not promote stereotyped behavior, but induced some episodes of grooming not statistically

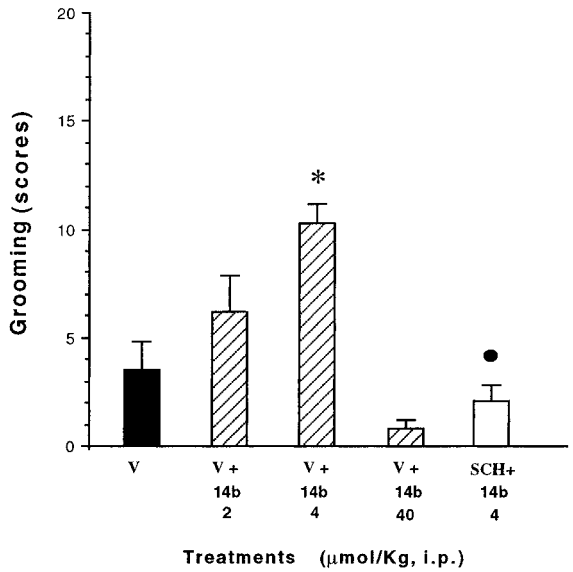


Figure 2. Effect of (*R*)-(+)-SCH 23390 on (+)-**14b**-induced grooming in rats. Vehicle [V, physiological (0.9%) saline] and (+)-**14b** were intraperitoneally (ip) injected 5 min before the test (30 min); V and (*R*)-(+)-SCH 23390 (SCH) at 1.8 μmol/kg were ip injected 25 min before V and (+)-**14b**. Histograms are the means ± SEM of the scores for grooming for each treatment group (at least eight animals). An asterisk (*) denotes results significantly different from those for vehicle-treated animals; a dot (●) denotes results significantly different from those for respective controls (Kruskal Wallis test followed by Mann Whitney *U* test).

different with respect to vehicle. A similar effect was reported previously for compounds which showed affinity for D_1 and D_2 receptors.[28]

In summary, this report describes a series of *trans*-2-amino-6-hydroxy-1-phenyl-2,3-dihydro-1*H*-indenes that in binding assays demonstrated affinity for both D_1 and D_2 DA receptor subtypes. These data indicate that the putative pharmacophore of the D_{1-like} receptor,[5] the 2-phenyl-2-(3-hydroxyphenyl)ethylamine **5**, embedded in these compounds in a *trans* extended conformation, does not induce high D_1 selectivity. On the other hand, the isomeric *trans*-2-amino-5-hydroxy-1-phenyl-2,3-dihydro-1*H*-indenes and the di-N-n-propyl derivatives, containing the 2-phenyl-2-(4-hydroxyphenyl)ethylamine moiety, showed high affinity and selectivity for D_1 receptor. In an "*in vivo*" behavioral study, (+)-**14b** and (+)-**15b** showed central D_1 agonistic activity. It is important to note that these compounds contain only a phenolic group, while most D_1 agonists known to date are catechol derivatives. These findings suggest that D_1 agonist activity does not require a catechol structure.

Experimental Section

Melting points were determined on a Buchi 510 apparatus and are uncorrected. Microanalyses were performed 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 200 MHz spectrometer. Chemical shifts are reported in parts per million (δ) downfield from the internal standard tetramethylsilane (Me_4Si). The IR spectra were run on a Perkin-Elmer Model 297 spectrometer as Nujol mulls or liquid films. The identity of all new compounds was confirmed by both elemental analysis and NMR data; homogeneity 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 by Merck-60 silica gel columns 70−230 mesh ASTM from Merck with a reported solvent. Optical rotations were obtained on a Perkin-Elmer 241 MC polarimeter.

(±)-*trans*-2-Amino-6-methoxy-1-phenyl-2,3-dihydro-1*H*-indene [(±)-6a] and (±)-*trans*-2-amino-5-methoxy-1-phenyl-2,3-dihydro-1*H*-indene [(±)-6b]. Under nitrogen, 5(6)-methoxy-3-phenyl-1*H*-indene (5.55 g, 25 mmol) was added to a stirred solution of $NaBH_4$ (0.4 g, 10.3 mmol) in dry diglyme (15 mL). The flask was cooled in an ice bath, and boron trifluoride etherate (1.95 g, 13.75 mmol) was added dropwise. The solution was stirred at room temperature for 3 h. Then hydroxylamine *O*-sulfonic acid (3.2 g, 27.5 mmol) in dry diglyme (15 mL) was added, and the mixture was heated at 100 °C for 3 h. The solution was cooled, treated with concentrated HCl (10 mL), and poured into water (100 mL). The acidic solution was extracted with Et_2O to remove diglyme and residue boronic acid, made basic with 2 N NaOH, and extracted with Et_2O. The extracts were dried and evaporated. To the residue, dissolved in absolute EtOH, was added concentrated HCl (1.7 mL). Evaporation of the solvent gave a white solid which was recrystallized. (±)-**6a**·HCl: mp 236−238 °C (from *i*-PrOH), yield 33%. (±)-**6b**·HCl: mp 220−222 °C (from EtOH abs), yield 31%. The hydrochloride was treated with 15% NH_4OH, and the amine was extracted with Et_2O. The extracts were dried and evaporated. The solid residue was recrystallized from Et_2O.

(±)-6a: mp 87−88 °C; ^{1}H NMR ($CDCl_3$) δ 7.28 (m, 5H, ArH), 6.76 (dd, 2H, H-5), 6.44 (d, 1H, H-7), 3.94 (d, 1H, J = 7.9 Hz, H-1), 3.70 (s, 3H, OCH_3), 3.64 (q, 1H, H-2), 3.14 (dd, 1H, H-3), 2.76 (dd, 1H, H-3), 2.14 (s, 2H, NH_2). Anal. ($C_{16}H_{17}NO$) C, H, N.

(±)-6b: mp 94−96 °C; ^{1}H NMR ($CDCl_3$) δ 7.28 (m, 5H, ArH), 6.81 (d, 1H, H-7), 6.78 (s, 1H, H-4), 6.70 (m, 1H, H-6), 3.82 (d, 1H, J = 8 Hz, H-1), 3.80 (s, 3H, OCH_3), 3.62 (q, 1H, H-2), 3.23 (dd, 1H, H-3), 2.85 (dd, 1H, H-3), 1.60 (s, 2H, NH_2). Anal. ($C_{16}H_{17}NO$) C, H, N.

Resolution of (±)-6a and (±)-6b. A solution of (−)-2,3-dibenzoyl-L-tartaric acid monohydrate (15.04 g, 40 mmol) in EtOH (60 mL) was added to a solution of (±)-**6a** (9.28 g, 39 mmol) in a mixture of EtOH (40 mL) and *i*-PrOH (60 mL). After standing at 0 °C for 24 h the solid was filtered and recrystallized from a mixture of EtOH (100 mL) and *i*-PrOH (40 mL). The colorless crystals (9.8 g) were recrystallized three times from a mixture of EtOH (100 mL) and *i*-PrOH (16 mL). (−)-2,3-Dibenzoyl-L-tartrate: mp 197−199 °C; $[\alpha]^{20}_D = -74.8$ (c = 1, MeOH). Anal. ($C_{16}H_{17}NO{\cdot}C_{18}H_{14}O_8$) C, H, N.

The crystalline salt was treated with an excess of 15% NH_4OH, and the solution was extracted with Et_2O (large volume). After being dried the extracts were evaporated to give (+)-*trans*-2-amino-6-methoxy-1-phenyl-2,3-dihydro-1*H*-indene (+)-**6a**, which was rectrystallized from Et_2O: mp 87−88 °C; $[\alpha]^{20}_D = +33.67$ (c = 1, EtOH); yield 2 g, 47%.

The ethanolic mother liquors from the preceding preparation of the (−)-2,3-dibenzoyl tartrate were concentrated *in vacuo*. A suspension of the residual solid in H_2O was made alkaline with 15% NH_4OH, and the mixture was extracted with Et_2O. Concentration of the extracts gave the free base. To a solution of this free base (3.2 g, 13 mmol) in a mixture of EtOH (20 mL) and *i*-PrOH (40 mL) was added a solution of (+)-2,3-dibenzoyl-L-tartaric acid (5.44 g, 14 mmol) in EtOH (40 mL). After 12 h at 0 °C the colorless crystals (5 g) were filtered and recrystallized three times from EtOH. (+)-2,3-Dibenzoyl-L-tartrate: mp 191−194 °C; $[\alpha]^{20}_D = +73.5$ (c = 1, MeOH). Anal. ($C_{16}H_{17}NO{\cdot}C_{18}H_{14}O_8$) C, H, N.

The crystalline salt was treated with an excess of 15% NH_4OH, and the solution was extracted with Et_2O (large volume). After being dried the extracts were evaporated to give (−)-*trans*-2-amino-6-methoxy-1-phenyl-2,3-dihydro-1*H*-indene [(−)-**6a**], which was rectrystallized from Et_2O: mp 87−88 °C; $[\alpha]^{20}_D = -33.27$ (c = 1, EtOH); yield 2.1 g, 51%.

A solution of (−)-2,3-dibenzoyl-L-tartaric acid monohydrate (15.04 g, 40 mmol) in EtOH (150 mL) was added to a solution of (±)-**6b** (9.28 g, 39 mmol) in EtOH (150 mL). After the mixture was left to stand at 0 °C for 24 h, the solid was filtered and recrystallized from a mixture of EtOH (190 mL) and MeOH (225 mL). The colorless crystals were recrystallized four times from EtOH. (−)-2,3-Dibenzoyl-L-tartrate: mp 195−

197 °C; $[\alpha]^{20}_D = -85.6$ ($c = 1$, MeOH); yield 2.7 g, 58%. Anal. ($C_{16}H_{17}NO \cdot C_{18}H_{14}O_8$) C, H, N.

The crystalline salt was treated with an excess of 15% NH_4OH, and the solution was extracted with Et_2O (large volume). After being dried the extracts were evaporated to give (+)-*trans*-2-amino-5-methoxy-1-phenyl-2,3-dihydro-1*H*-indene [(+)-**6b**], which was recrystallized from Et_2O: mp 93−96 °C; $[\alpha]^{20}_D = +16.74$ ($c = 1$, EtOH); yield 2.7 g, 58%.

The ethanolic mother liquors from the preceding preparation of the (−)-2,3-dibenzoyl tartrate were concentrated *in vacuo*. A suspension of the residual solid in H_2O was made alkaline with 15% NH_4OH, and the mixture was extracted with Et_2O. Concentration of the extracts gave the free base. To a solution of this free base (5.80 g, 21 mmol) in MeOH (200 mL) was added a solution of (+)-2,3-dibenzoyl-L-tartaric acid (9.03 g, 25 mmol) in EtOH (200 mL). After 12 h at 0 °C the colorless crystals were filtered and recrystallized three times from EtOH/MeOH, 1/1. (+)-2,3-Dibenzoyl-L-tartrate: mp 195−196 °C; $[\alpha]^{20}_D = -83.6$ ($c = 1$, MeOH). Anal. ($C_{16}H_{17}NO \cdot C_{18}H_{14}O_8$) C, H, N.

The crystalline salt was treated with an excess of 15% NH_4OH, and the solution was extracted with Et_2O (large volume). After being dried, the extracts were evaporated to give (−)-*trans*-2-amino-5-methoxy-1-phenyl-2,3-dihydro-1*H*-indene [(−)-**6b**], which was recrystallized from Et_2O: mp 93−96 °C; $[\alpha]^{20}_D = -16.9$ ($c = 1$, EtOH); yield 2.8 g, 68%.

Determination of the Enantiomeric Excess of the Amines (+)-6a, (−)-6a, (+)-6b, and (−)-6b. Racemic and enantiomeric amines were derivatized with (*R*)-1-(1-naphthyl)-ethyl isocyanate as described by Cannon.[14] Ureas were purified by column chromatography on silica gel with EtOAc/*n*-hexane/*i*-PrOH (2/8/0.5) as eluent. NMR spectrum of racemic urea obtained from (±)-**6a** showed two doublet at 3.98 and 3.90 ppm (indene H-1 proton) and two doublet at 1.52 and 1.41 ppm (methyl protons). The NMR spectrum of the racemic urea obtained from **(±)-6b** showed two doublets at 3.94 and 3.85 ppm (indene H-1 proton) and two doublets at 1.52 and 1.42 ppm (methyl protons).

1-(6(5)-Methoxy-1-phenyl-2,3-dihydro-1*H*-inden-2-yl)-3-(1-naphthalen-1-ylethyl)ureas (7a,b, 8a,b). Inspection and integration of the benzylic and methyl protons signals in the NMR spectra provided an enantiomeric excess ≥98%.

7a was obtained from (+)-**6a**: mp 202−203 °C; $[\alpha]^{20}_D = -24.6$ ($c = 1$, EtOH); yield 88%; ^{1}H NMR ($CDCl_3$) δ 8.11, 7.88 and 7.78 (three m, 3H, ArH), 7.52 and 7.38 (two m, 4H, ArH), 7.10 (m, 4H, ArH), 6.90 (m, 2H, ArH), 6.72 (dd, 1H, ArH), 6.38 (d, 1H, ArH), 5.55 (m, 1H, naphth-CH), 4.69 and 4.50 (two d, 2H, NH), 4.27 (m, 1H, H-2), 3.90 (d, 1H, H-1), 3.68 (s, 3H, OCH_3), 3.34 and 2.61 (two dd, 2H, H-3), 1.52 (d, 3H, CH_3). Anal. ($C_{29}H_{28}N_2O_5$) C, H, N.

8a was obtained from (−)-**6a**: mp 190−191 °C; $[\alpha]^{20}_D = -23.3$ ($c = 1$, EtOH); yield 89%; ^{1}H NMR ($CDCl_3$) δ 8.06, 7.83 and 7.75 (three m, 3H, ArH), 7.49 (m, 2H, ArH), 7.32 (m, 5H, ArH), 7.13 (m, 3H, ArH), 6.72 (dd, 1H, ArH), 6.40 (d, 1H, ArH), 5.53 (m, 1H, naphth-CH), 4.66 and 4.43 (two d, 2H, NH), 4.25 (m, 1H, H-2), 3.98 (d, 1H, H-1), 3.68 (s, 3H, OCH_3), 3.28 and 2.56 (two dd, 2H, H-3), 1.41 (d, 3H, CH_3). Anal. ($C_{29}H_{28}N_2O_5$) C, H, N.

7b was obtained from **(+)-6b**: mp 218−219 °C; $[\alpha]^{20}_D = -22.5$ ($c = 1$, EtOH); yield 88%; ^{1}H NMR ($CDCl_3$) δ 8.10, 7.88 and 7.78 (three m, 3H, ArH), 7.51 and 7.38 (two m, 4H, ArH), 7.08 (m, 3H, ArH), 6.89 (m, 2H, ArH), 6.70 (m, 3H, ArH), 5.56 (m, 1H, naphth-CH), 4.52 (bs, 2H, NH), 4.24 (m, 1H, H-2), 3.85 (d, 1H, H-1), 3.78 (s, 3H, OCH_3), 3.37 and 2.65 (two dd, 2H, H-3), 1.52 (d, 3H, CH_3). Anal. ($C_{29}H_{28}N_2O_5$) C, H, N.

8b was obtained from (−)-**6b**: mp 203−204 °C; $[\alpha]^{20}_D = +10$ ($c = 1$, EtOH); yield 80%; ^{1}H NMR ($CDCl_3$) δ 8.05, 7.83, and 7.74 (three m, 3H, ArH), 7.48 and 7.38 (two m, 4H, ArH), 7.28 (m, 3H, ArH), 7.12 (m, 2H, ArH), 6.71 (m, 3H, ArH), 5.53 (m, 1H, naphth-CH), 4.62 and 4.41 (two bs, 2H, NH), 4.23 (m, 1H, H-2), 3.94 (d, 1H, H-1), 3.78 (s, 3H, OCH_3), 3.32 and 2.61 (two dd, 2H, H-3), 1.42 (d, 3H, CH_3). Anal. ($C_{29}H_{28}N_2O_5$) C, H, N.

***trans*-6-Methoxy-1-phenyl-2-(di-*n*-propylamino)-2,3-dihydro-1*H*-indene Hydrochlorides [(+)-9a, (−)-9a] and *trans*-5-methoxy-1-phenyl-2-(di-*n*-propylamino)-2,3-dihydro-1*H*-indene Hydrochlorides [(+)-9b, (−)-9b].** The N-alkylation of amines **(+)-6a**, (−)-**6a**, **(+)-6b**,and (−)-**6b** was accomplished as described by Marchini et al.[15] The amine (2 g, 8.4 mmol) was allowed to react with sodium borohydride (3.15 g, 84 mmol) and propionic acid (10.4 g, 140 mmol) in dry benzene (40 mL). The oily residue was chromatographed on silica gel column eluted with EtOAc/cyclohexane, 75/25 [(+)-**9a**, (−)-**9a**] or EtOAc [(+)-**9b**, (−)-**9b**]. The hydrochlorides were prepared by addition of 37% HCl to a solution of the base in EtOH. The solvent was evaporated under reduced pressure, and the residue was recrystallized from EtOAc/ Et_2O.

(+)-**9a·HCl** was obtained from (−)-**6a**: mp 148−151 °C; $[\alpha]^{20}_D = +64.35$ ($c = 1$, EtOH); yield 50%; ^{1}H NMR (DMSO-d_6) δ 10.74 (bs, 1H, NH), 7.40 (m, 5H, ArH), 7.27 (d, 1H, H-4), 6.85 (dd, 1H, H-5), 6.15 (d, 1H, H-7), 4.86 (d, 1H, H-1), 4.50 (m, 1H, H-2), 3.62 (s, 3H, OCH_3), 3.51 and 3.32 (two m, 2H, H-3), 3.0 (m, 4H, NCH_2C), 1.68 and 1.37 (two m, 4H, $NCCH_2$), 0.89 and 0.53 (two t, 6H, CH_3). Anal. ($C_{22}H_{30}ClNO$) C, H, N.

(−)-**9a·**HCl was obtained from (+)-**6a**: mp 148−151 °C; $[\alpha]^{20}_D = -64.03$ ($c = 1$, EtOH); yield 55%. The NMR spectrum was the same as that of (+)-**9a·**HCl. Anal. ($C_{22}H_{30}ClNO$) C, H, N.

(+)-**9b·**HCl was obtained from (−)-**6b**: mp 159−160 °C; $[\alpha]^{20}_D = +88.98$ ($c = 1$, EtOH); yield 50%; ^{1}H NMR (DMSO-d_6) δ 11.0 (bs, 1H, NH), 7.37 (m, 5H, ArH), 6.90 (d, 1H, H-4), 6.72 (dd, 1H, H-6), 6.53 (d, 1H, H-7), 4.81 (d, 1H, H-1), 4.49 (m, 1H, H-2), 3.75 (s, 3H, OCH_3), 3.56 and 3.39 (two m, 2H, H-3), 2.98 (m, 4H, NCH_2C), 1.68 and 1.36 (two m, 4H, $NCCH_2$), 0.88 and 0.53 (two t, 6H, CH_3). Anal. ($C_{22}H_{30}ClNO$) C, H, N.

(−)-**9b·**HCl was obtained from **(+)-6b**: mp 159−160 °C; $[\alpha]^{20}_D = -89.5$ ($c = 1$, EtOH); yield 45%. The NMR spectrum was the same as that of (+)-**9b·**HCl. Anal. ($C_{22}H_{30}ClNO$) C, H, N.

***trans*-6-Methoxy-1-phenyl-2-[(ethoxycarbonyl)amino]-2,3-dihydro-1*H*-indenes [(+)-10a, (−)-10a] and *trans*-5-methoxy-1-phenyl-2-[(ethoxycarbonyl)amino]-2,3-dihydro-1*H*-indenes [(+)-10b, (−)-10b].** A solution of ethyl chloroformate (1.18 g, 11 mmol) in anhydrous Et_2O (15 mL) was added dropwise to a solution of the amines (+)-**6a**, (−)-**6a**, (+)-**6b**,and (−)-**6b** (2.6 g, 11 mmol) in anhydrous Et_2O (70 mL) and triethylamine (3.1 mL, 22 mmol), cooled at 0 °C. The reaction mixture was allowed to reach room temperature and then stirred for 1 h. Water was then added, and the aqueous solution was extracted with three portions of $CHCl_3$. The combined organic phases were dried and evaporated. The solid residue was recrystallized.

(+)-**10a** was obtained from (+)-**6a**: mp 95−96 °C (from cyclohexane); $[\alpha]^{20}_D = +15.4$ ($c = 1$, EtOH); yield 92%; ^{1}H NMR ($CDCl_3$) δ 7.27 (m, 6H, ArH), 6.80 (dd, 1H, H-5), 6.53 (d, 1H, H-7), 4.94 (bs, 1H, NH), 4.34 (m, 1H, H-2), 4.10 (m, 3H, H-1, OCH_2), 3.72 (s, 3H, OCH_3), 3.36 (dd, 1H, H-3), 2.74 (dd, 1H, H-3), 1.20 (t, 3H, CH_3). Anal. ($C_{19}H_{21}NO_3$) C, H, N.

(−)-**10a** was obtained from (−)-**6a**: mp 95−96 °C (from cyclohexane); $[\alpha]^{20}_D = -14.95$ (c = 1, EtOH); yield 87%. The NMR spectrum was the same as that of **(+)-10a**. Anal. ($C_{19}H_{21}NO_3$) C, H, N.

(+)-**10b** was obtained from (−)-**6b**: mp 174−176 °C (from *i*-PrOH); $[\alpha]^{20}_D = +16.1$ ($c = 1$, EtOH); yield 81%; ^{1}H NMR ($CDCl_3$) δ 7.23 (m, 5H, ArH), 6.85 (m, 2H, ArH), 6.75 (dd, 1H, H-6), 4.94 (bs, 1H, NH), 4.35 (m, 1H, H-2), 4.09 (m, 3H, H-1, OCH_2), 3.82 (s, 3H, OCH_3), 3.40 (dd, 1H, H-3), 2.80 (dd, 1H, H-3), 1.22 (t, 3H, CH_3). Anal. ($C_{19}H_{21}NO_3$) C, H, N.

(−)-**10b** was obtained from **(+)-6b**: mp 174−176 °C (from i-PrOH); $[\alpha]^{20}_D = -15.62$ ($c = 1$, EtOH); yield 81%. The NMR spectrum was the same as that of (+)-**10b**. Anal. ($C_{19}H_{21}NO_3$) C, H, N.

***trans*-6-Methoxy-2-(methylamino)-1-phenyl-2,3-dihydro-1*H*-indene Hydrochlorides [(+)-11a, (−)-11a] and *trans*-5-methoxy-2-(methylamino)-1-phenyl-2,3-dihydro-1*H*-indene Hydrochlorides [(+)-11b, (−)-11b].** A solution of the compounds (+)-**10a**, (−)-**10a**, (+)-**10b**, and (−)-**10b** (3 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. To the oily residue, dissolved in EtOH (60 mL), was added 37% HCl (1.6 mL). The solid obtained after evaporation of the solvent was recrystallized.

(+)-**11a**·HCl was obtained from (−)-**10a**: mp 182−184 °C (from *i*-PrOH/Et_2O); $[\alpha]^{20}_D = +26.3$ ($c = 1$, EtOH); yield 73%; ^{1}H NMR (DMSO-d_6) δ 9.52 and 9.32 (two bs, 2H, NH_2^+), 7.33 (m, 6H, ArH), 6.86 (dd, 1H, H-5), 6.36 (d, 1H, H-7), 4.66 (d, 1H, H-1), 4.0 (m, 1H, H-2), 3.65 (s, 3H, OCH_3), 3.30 (dd, 1H, H-3), 3.10 (dd, 1H, H-3), 2.53 (s, 3H, CH_3). Anal. ($C_{17}H_{20}$ClNO) C, H, N.

(−)-**11a**·HCl was obtained from (+)-**10a**: mp 182−184 °C (from *i*-PrOH/Et_2O); $[\alpha]^{20}_D = -26.10$ ($c = 1$, EtOH); yield 72%. The NMR spectrum was the same as that of (+)-**11a**·HCl. Anal. ($C_{17}H_{20}$ClNO) C, H, N.

(+)-**11b**·HCl was obtained from (+)-**10b**: mp 239−241 °C (from *i*-PrOH); $[\alpha]^{20}_D = +52.16$ ($c = 1$, EtOH); yield 75%. ^{1}H NMR (DMSO-d_6) δ 9.59 and 9.40 (two bs, 2H, NH_2^+), 7.33 (m, 5H, ArH), 6.95 (d, 1H, H-4), 6.75 (m, 2H, ArH), 4.62 (d, 1H, H-1), 4.01 (m, 1H, H-2), 3.76 (s, 3H, OCH_3), 3.45 (dd, 1H, H-3), 3.18 (dd, 1H, H-3), 2.52 (s, 3H, CH_3). Anal. ($C_{17}H_{20}$ClNO) C, H, N.

(−)-**11b**·HCl was obtained from (−)-**10b**: mp 239−241 °C (from *i*-PrOH); $[\alpha]^{20}_D = -51.79$ ($c = 1$, EtOH); yield 73%. The NMR spectrum was the same as that of (+)-**11b**·HCl. Anal. ($C_{17}H_{20}$ClNO) C, H, N.

***trans*-*N*-Methyl-*N*-allyl-2-amino-6-methoxy-1-phenyl-2,3-dihydro-1*H*-indene Hydrochlorides [(+)-12a, (−)-12a] and *trans*-*N*-methyl-*N*-allyl-2-amino-5-methoxy-1-phenyl-2,3-dihydro-1*H*-indene Hydrochlorides [(+)-12b, (−)-12b].** A mixture of the hydrochlorides (+)-**11a**, (−)-**11a**, (+)-**11b**, and (−)-**11b** (1.5 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 vacuum, H_2O 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 EtOAc as eluent. The desired fraction was collected and evaporated, the residue was dissolved in EtOH (35 mL), and 37% HCl (1.3 mL) was added. The solid obtained after evaporation of the solvent was recrystallized from EtOAc/Et_2O.

(+)-**12a**·HCl was obtained from (+)-**11a**·HCl: mp 198−200 °C; $[\alpha]^{20}_D = +57.0$ ($c = 1$, EtOH); yield 65%. ^{1}H NMR (DMSO-d_6) δ 11.67 (bs, 1H, NH^+), 7.33 (m, 6H, ArH), 6.84 (d, 1H, H-7), 6.30 (dd, 1H, H-5), 5.92 (m, 1H, CH═), 5.40 (m, 2H, ═CH_2), 4.91 (d, 1H, H-1), 4.28 (m, 1H, H-2), 3.77 (m, 1H, H-3), 3.61 (s, 3H, OCH_3), 3.46 (m, 3H, H-3, NCH_2), 2.60 and 2.52 (two d, 3H, CH_3). Anal. ($C_{20}H_{24}$ClNO) C, H, N.

(−)-**12a**·HCl was obtained from (−)-**11a**·HCl: mp 198−200 °C; $[\alpha]^{20}_D = +57.30$ ($c = 1$, EtOH); yield 64%.The NMR spectrum was the same as that of (+)-**12a**·HCl. Anal. ($C_{20}H_{24}$ClNO) C, H, N.

(+)-**12b**·HCl was obtained from **(+)-11b**·HCl: mp 68−70 °C; $[\alpha]^{20}_D = +80.22$ ($c = 1$, EtOH); yield 74%. ^{1}H NMR (DMSO-d_6) δ 11.53 (bs, 1H, NH^+), 7.34 (m, 5H, ArH), 6.93 (d, 1H, H-4), 6.71 (m, 2H, ArH), 5.93 (m, 1H, CH═), 5.40 (m, 2H, ═CH_2), 4.82 (d, 1H, H-1), 4.28 (m, 1H, H-2), 3.80 (m, 1H, H-3), 3.72 (s, 3H, OCH_3), 3.49 (m, 3H, H-3, NCH_2), 3.37 (m, 1H, H-3), 2.62 and 2.53 (two d, 3H, CH_3). Anal. ($C_{20}H_{24}$ClNO) C, H, N.

(−)-**12b**·HCl was obtained from (−)-**11b**·HCl: mp 68−70 °C; $[\alpha]^{20}_D = -79.90$ ($c = 1$, EtOH); yield 70%. The NMR spectrum was the same as (+)-**12b**·HCl. Anal. ($C_{20}H_{24}$ClNO) C, H, N.

***trans*-*N*-Methyl-*N*-*n*-propyl-2-amino-6-methoxy-1-phenyl-2,3-dihydro-1*H*-indene Hydrochlorides [(+)-13a, (−)-13a] and *trans*-*N*-methyl-*N*-propyl-2-amino-5-methoxy-1-phenyl-2,3-dihydro-1*H*-indene Hydrochlorides [(+)-13b, (−)-13b].** A mixture of the hydrochlorides (+)-**11a**, (−)-**11a**, (+)-**11b**, and (−)-**11b** (1.5 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 solvent in vacuum, 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 EtOAc as eluent. The desired fraction was collected and evaporated. The residue was dissolved in EtOH (35 mL), and 37% HCl (1.3 mL) was added. The solid obtained after evaporation of the solvent was recrystallized from EtOAc/Et_2O.

(+)-**13a**·HCl was obtained from (+)-**11a**·HCl: mp 175−176 °C; $[\alpha]^{20}_D = +60.10$ ($c = 1$, EtOH); yield 86%; ^{1}H NMR (DMSO-d_6) δ 11.17 and 11.01 (two bs, 1H, NH^+), 7.33 (m, 6H, ArH), 6.84 (dd, 1H, H-5), 6.28 (d, 1H, H-7), 4.85 (m, 1H, H-1), 4.34 (m, 1H, H-2), 3.62 (s, 3H, OCH_3), 3.41 (m, 2H, H-3), 2.98 (m, 2H, NCH_2), 2.69 and 2.60 (two d, 3H, NCH_3), 1.65 and 1.43 (two m, 2H, CCH_2C), 0.88 and 0.64 (two t, 3H, CH_3). Anal. ($C_{20}H_{26}$ClNO) C, H, N.

(−)-**13a**·HCl was obtained from (−)-**11a**·HCl: mp 175−176 °C; $[\alpha]^{20}_D = -60.40$ ($c = 1$, EtOH); yield 90%. The NMR spectrum was the same as that of (+)-**13a**·HCl. Anal. ($C_{20}H_{26}$ClNO) C, H, N.

(+)-**13b**·HCl was obtained from **(+)-11b**·HCl: mp 150−152 °C; $[\alpha]^{20}_D = +78.30$ ($c = 1$, EtOH); yield 89%. ^{1}H NMR (DMSO-d_6) δ 11.17 and 11.0 (two bs, 1H, NH^+), 7.38 (m, 5H, ArH), 6.96 (d, 1H, H-4), 6.72 (m, 2H, H-6,7), 4.81 (d, 1H, H-1), 4.38 (m, 1H, H-2), 3.76 (s, 3H, OCH_3), 3.44 (m, 2H, H-3), 2.98 (m, 2H, NCH_2), 2.72 and 2.64 (two d, 3H, NCH_3), 1.69 and 1.42 (two m, 2H, CCH_2C), 0.90 and 0.68 (two t, 3H, CH_3). Anal. ($C_{20}H_{26}$ClNO) C, H, N.

(−)-**13b**·HCl was obtained from (−)-**11b**·HCl: mp 150−152 °C; $[\alpha]^{20}_D = -77.60$ ($c = 1$, EtOH); yield 86%. The NMR spectrum was the same as that of (+)-**13b**·HCl. Anal. ($C_{20}H_{26}$ClNO) C, H, N.

General Procedure for the Demethylation. Methanesulfonic acid (71 mL) and methionine (9.8 g, 65.7 mmol) were added to a solution of the metoxyamine hydrochloride (1.6 g, 5.8 mmol) in water (4.5 mL). The mixture was stirred at 25 °C for 4 days, then poured into ice−water (80 mL), and made basic (pH = 8) with 15% NH_4OH. The mixture was extracted with EtOAc. The organic extracts, washed with aqueous $NaHSO_3$ and water, were dried and evaporated. The residue was dissolved in EtOH (20 mL), and 37% HCl (0.9 mL) was added. The solid obtained after evaporation of the solvent was recrystallized.

***trans*-2-Amino-6-hydroxy-1-phenyl-2,3-dihydro-1*H*-indene Hydrochlorides [(+)-14a and (−)-14a].** **(+)-14a**·HCl was obtained from (−)-**6a**·HCl: mp 249−251 °C (from EtOAc/Et_2O); $[\alpha]^{20}_D = +5.30$ ($c = 1$, EtOH); yield 70%; ^{1}H NMR (DMSO-d_6) δ 9.30 (bs, 1H, OH), 8.49 (bs, 3H, NH_3^+), 7.30 (m, 5H, ArH), 7.13 (d, 1H, H-4), 6.68 (dd, 1H, H-5), 6.23 (d, 1H, H-7), 4.44 (d, 1H, H-1), 3.88 (m, 1H, H-2), 3.32 (dd, 1H, H-3), 2.97 (dd, 1H, H-3). Anal. ($C_{15}H_{16}$ClNO) C, H, N.

(−)-**14a**·HCl was obtained from (+)-**6a**·HCl: mp 249−251 °C (from EtOAc/Et_2O); $[\alpha]^{20}_D = -5.21$ ($c = 1$, EtOH); yield 66%. The NMR spectrum was the same as that of (+)-**14a**·HCl. Anal. ($C_{15}H_{16}$ClNO) C, H, N.

***trans*-2-Amino-5-hydroxy-1-phenyl-2,3-dihydro-1*H*-indene Hydrochlorides [(+)-14b and (−)-14b].** **(+)-14b**·HCl was obtained from (−)-**6b**·HCl: mp 245−247 °C (from *i*-PrOH/Et_2O); $[\alpha]^{20}_D = +17.72$ ($c = 1$, EtOH); yield 44%; ^{1}H NMR (DMSO-d_6) δ 9.46 (s, 1H, OH), 8.46 (bs, 3H, NH_3^+), 7.33 (m, 3H, ArH), 7.18 (m, 2H, ArH), 6.73 (d, 1H, H-4), 6.62 (m, 2H, H-6,7), 4.37 (d, 1H, H-1), 3.88 (m, 1H, H-2), 3.35 (m, 1H, H-3), 2.94 (m, 1H, H-3). Anal. ($C_{15}H_{16}$ClNO) C, H, N.

(−)-**14b**·HCl was obtained from (+)-**6b**·HCl: mp 245−247 °C (from *i*-PrOH/Et_2O); $[\alpha]^{20}_D = -17.60$ ($c = 1$, EtOH); yield 48%. The NMR spectrum was the same as that of (+)-**14b**·HCl. Anal. ($C_{15}H_{16}$ClNO) C, H, N.

***trans*-*N*,*N*-Di-*n*-propyl-2-amino-6-hydroxy-1-phenyl-2,3-dihydro-1*H*-indene Hydrochlorides [(+)-15a, (−)-15a].** **(+)-15a**·HCl was obtained from (+)-**9a**·HCl: mp 226−228 °C (from EtOAc/Et_2O); $[\alpha]^{20}_D = +70.0$ ($c = 1$, EtOH); yield 86%; ^{1}H NMR (DMSO-d_6) δ 10.80 (bs, 1H, NH^+), 9.26 (s, 1H, OH), 7.40 (m, 5H, ArH), 7.10 (d, 1H, H-4), 6.66 (dd, 1H, H-5), 6.02 (d, 1H, H-7), 4.80 (d, 1H, H-1), 4.45 (m, 1H, H-2), 3.45 (m, 1H, H-3), 3.24 (m, 1H, H-3), 2.92 (m, 4H, N-CH_2), 1.65 and 1.32 (two m, 4H, $NCCH_2$), 0.88 and 0.52 (two t, 6H, CH_3). Anal. ($C_{21}H_{28}$ClNO) C, H, N.

(−)-**15a**·HCl was obtained from (−)-**9a**·HCl: mp 226−228 °C (from EtOAc/Et_2O); $[\alpha]^{20}_D = -69.60$ ($c = 1$, EtOH); yield

58%. The NMR spectrum was the same as (+)-**15a**·HCl. Anal. ($C_{21}H_{28}ClNO$) C, H, N.

***trans*-*N*,*N*-Di-*n*-propyl-2-amino-5-hydroxy-1-phenyl-2,3-dihydro-1*H*-indene Hydrochlorides [(+)-15b, (−)-15b].** (+)-**15b**·HCl was obtained from (+)-**9b**·HCl: mp 237−239 °C (from *i*-PrOH); $[\alpha]^{20}_D = +86.87$ ($c = 1$, EtOH); yield 58%; ^{1}H NMR (DMSO-d_6) δ 11.16 (bs, 1H, NH^+), 9.48 (s, 1H, OH), 7.40 (m, 5H, ArH), 6.72 (d, 1H, H-4), 6.58 (dd, 1H, H-6), 6.40 (d, 1H, H-7), 4.78 (d, 1H, H-1), 4.40 (m, 1H, H-2), 3.41 (m, 2H, H-3), 2.94 (m, 4H, N-CH_2), 1.65 and 1.32 (two m, 4H, NCCH_2), 0.90 and 0.52 (two t, 6H, CH_3). Anal. ($C_{21}H_{28}ClNO$) C, H, N.

(−)-**15b**·HCl was obtained from (−)-**9b**·HCl: mp 238−239 °C (from *i*-PrOH); $[\alpha]^{20}_D = -87.21$ ($c = 1$, EtOH); yield 58%. The NMR spectrum was the same as (+)-**15b**·HCl. Anal. ($C_{21}H_{28}ClNO$) C, H, N.

***trans*-*N*-Methyl-*N*-allyl-2-amino-6-hydroxy-1-phenyl-2,3-dihydro-1*H*-indene Hydrochlorides [(+)-16a, (−)-16a].** (+)-**16a**·HCl was obtained from (+)-**12a**·HCl: mp 107−109 °C (from EtOH/Et_2O, hygroscopic); $[\alpha]^{20}_D = +64.20$ ($c = 1$, EtOH); yield 71%; ^{1}H NMR (DMSO-d_6) δ 11.18 (bs, 1H, NH^+), 9.30 (s, 1H, OH), 7.35 (m, 5H, ArH), 7.13 (d, 1H, H-4), 6.67 (dd, 1H, H-7), 6.18 (m, 1H, H-5), 5.88 (m, 1H, CH═), 5.41 (m, 2H, CH_2═), 4.81 (d, 1H, H-1), 4.30 (m, 1H, H-2), 3.68 (m, 1H, H-3), 3.48 (m, 3H, H-3, N-CH_2), 2.69 and 2.53 (two d, 3H, CH_3). Anal. ($C_{19}H_{22}ClNO$) C, H, N.

(−)-**16a**·HCl was obtained from (−)-**12a**·HCl: mp 107−109 °C (from EtOH/Et_2O, hygroscopic); $[\alpha]^{20}_D = -64.30$ ($c = 1$, EtOH); yield 72%. The NMR spectrum was the same as that of (+)-**16a**·HCl. Anal. ($C_{19}H_{22}ClNO$) C, H, N.

***trans*-*N*-Methyl-*N*-allyl-2-amino-5-hydroxy-1-phenyl-2,3-dihydro-1*H*-indene Hydrochlorides [(+)-16b, (−)-16b].** (+)-**16b**·HCl was obtained from (+)-**12b**·HCl: mp 87−89 °C (from EtOAc/Et_2O); $[\alpha]^{20}_D = +75.93$ ($c = 1$, EtOH); yield 74%; ^{1}H NMR (DMSO-d_6) δ 11.39 (bs, 1H, NH^+), 9.50 (s, 1H, OH), 7.32 (m, 5H, ArH), 6.71 (d, 1H, H-4), 6.58 (m, 2H, H-6,7), 5.89 (m, 1H, CH═), 5.42 (m, 2H, CH_2═), 4.78 (d, 1H, H-1), 4.22 (m, 1H, H-2), 3.77 (m, 2H, H-3), 3.40 (m, 2H, N-CH_2), 2.63 and 2.53 (two d, 3H, CH_3). Anal. ($C_{19}H_{22}ClNO$) C, H, N.

(−)-**16b**·HCl was obtained from (−)-**12b**·HCl: mp 86−88 °C (from EtOAc/Et_2O); $[\alpha]^{20}_D = -76.70$ ($c = 1$, EtOH); yield 84%. The NMR spectrum was the same as that of (+)-**16b**·HCl. Anal. ($C_{19}H_{22}ClNO$) C, H, N.

***trans*-*N*-Methyl-*N*-*n*-propyl-2-amino-6-hydroxy-1-phenyl-2,3-dihydro-1*H*-indene Hydrochlorides [(+)-17a, (−)-17a].** (+)-**17a**·HCl was obtained from (+)-**13a**·HCl: mp 117−119 °C (from EtOH/Et_2O, hygroscopic); $[\alpha]^{20}_D = +64.40$ ($c = 1$, EtOH); yield 69%; ^{1}H NMR (DMSO-d_6) δ 10.83 and 10.71 (two bs, 1H, NH^+), 9.30 (s, 1H, OH), 7.34 (m, 5H, ArH), 7.14 (d, 1H, H-4), 6.67 (dd, 1H, H-5), 6.12 (m, 1H, H-7), 4.76 (d, 1H, H-1), 4.36 (m, 1H, H-2), 3.33 (m, 2H, H-3), 3.0 (m, 2H, N-CH_2), 2.75 and 2.60 (two d, 3H, NCH_3), 1.65 and 1.41 (two m, 2H, CCH_2C), 0.90 and 0.66 (two t, 3H, CH_3). Anal. ($C_{19}H_{24}ClNO$) C, H, N.

(−)-**17a**·HCl was obtained from (−)-**13a**·HCl: mp 117−119 °C (from EtOH/Et_2O, hygroscopic); $[\alpha]^{20}_D = -64.60$ ($c = 1$, EtOH); yield 73%. The NMR spectrum was the same as that of (+)-**17a**·HCl. Anal. ($C_{19}H_{24}ClNO$) C, H, N.

***trans*-*N*-Methyl-*N*-propyl-2-amino-5-hydroxy-1-phenyl-2,3-dihydro-1*H*-indene Hydrochlorides [(+)-17b, (−)-17b].** (+)-**17b**·HCl was obtained from (+)-**13b**·HCl: mp 128−130 °C (from EtOAc/Et_2O); $[\alpha]^{20}_D = +75.50$ ($c = 1$, EtOH); yield 74%; ^{1}H NMR (DMSO-d_6) δ 11.18 and 11.04 (two bs, 1H, NH^+), 9.47 (s, 1H, OH), 7.31 (m, 5H, ArH), 6.72 (d, 1H, H-4), 6.55 (m, 2H, H-6,7), 4.72 (m, 1H, H-1), 4.29 (m, 1H, H-2), 3.40 (m, 2H, H-3), 2.98 (m, 2H, N-CH_2), 2.69 and 2.59 (two d, 3H, NCH_3), 1.67 and 1.43 (two m, 2H, CCH_2C), 0.88 and 0.63 (two t, 3H, CH_3). Anal. ($C_{19}H_{24}ClNO$) C, H, N.

(−)-**17b**·HCl was obtained from (−)-**13b**·HCl: mp 128−130 °C (from EtOAc/Et_2O); $[\alpha]^{20}_D = -76.40$ ($c = 1$, EtOH); yield 76%. The NMR spectrum was the same as that of (+)-**17b**·HCl. Anal. ($C_{19}H_{22}ClNO$) C, H, N.

Pharmacology. Materials. (*R*)-(+)-SCH 23390 hydrochloride, (±)-PPHT hydrochloride, and (*R*)-(+)-SK&F 38393 hydrochloride were purchased from Research Biochemicals International (Natick, MA). Dopamine was purchased from Sigma Chemical Co. (St. Louis, MO). [^{3}H]Spiperone and [^{3}H]-SCH 23390 were purchased from Amersham Radiochemical Centre (Buckinghamshire, UK). All substances employed in the binding assays were dissolved in distilled water. For behavioral tests the compounds were dissolved in physiological (0.9%) saline and injected intraperitoneally (ip).

Animals. In the radioligand-binding studies striata were obtained from male Sprague−Dawley rats (250−300 g body weight) obtained from Charles River (Calco, Italy). Behavioral studies were performed on male Wistar rats (Morini, S. Polo d'Enza, Italy) weighing 250−280 g.

Receptor Binding. The compounds were evaluated for their *in vitro* binding affinity at the D_1 receptor with [^{3}H]SCH 23390 (70 Ci/mmol, 0.25 nM) as a ligand, and at the D_2 receptor using [^{3}H]spiperone (42 Ci/mmol, 0.25 nM) as a ligand. Binding experiments were performed according to the protocol detailed in a former study of our group.[17]

Behavioral Studies. Animals were housed in groups of four with food and water available ad libitum, and a 24 h light cycle, from 7 a.m. to 7 p.m., for at least 1 week prior to the start of the tests. All the behavioral procedures were performed between 9 a.m. and 1 p.m. in a soundproof, air-conditioned room, the animals being monitored by trained observers unaware of the experimental design. Twenty minutes before the start of the experiments, the animals were transferred, in groups of four, to glass observation cages (40 × 30 × 34 cm) to accustom them to the new environment. The test started immediately after the last treatment and lasted 30 min.

The experiments were replicated on separate days using new groups of animals. Grooming was evaluated according to Gispen et al.[29] In brief, an observer recorded every 15 s whether or not each rat displayed the phenomenon defined as follows: face and body washing, scratching, licking paws or tail. If one of these signs was observed, a positive score was given. In the case of antagonism experiments, the dose used for SCH 23390 was chosen on the basis of previous works[24] and was "per se" ineffective to modify the behaviour in question with respect to saline injection. Data for grooming are presented as mean ± SEM of the cumulative scores for each animal during the test period and were analyzed using Kruskal Wallis test followed by Mann Whitney *U* test, with the level of significance set at $p < 0.05$.

Acknowledgment. This work was supported by University of Camerino. Dr Barili is recipient of an Italian National Researchs Council fellowship (Special Project Aging).

References

(1) Sibley, D. R.; Monsma, J. F., Jr. Molecular biology of dopamine receptors. *Trends Pharmacol. Sci.* **1992**, *13*, 61−69.
(2) Hyttel, J. SCH 23390 - The First Selective Dopamine D_1 Antagonist. *Eur. J. Pharmacol.* **1983**, *91*, 153−154.
(3) Berger, J. G.; Changh, W. K.; Clader, J. W.; Hou, D.; Chipkin, R. E.; McPhail, A.T. Synthesis and Receptor Affinities of Some Conformationally Restricted Analogues of the Dopamine D_1 Selective Ligand (5R)-8-Chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1*H*-3-benzazepin-7-ol. *J. Med. Chem.* **1989**, *32*, 1913−1921.
(4) Barnett, A.; McQuade, R. D.; Tedford, C. Highlights of D_1 Dopamine Receptor Antagonist Research. *Neurochem. Int.* **1992**, *20*, Suppl., 119S−122S.
(5) Brewster, W. K.; Nichols, D. E.; Riggs, R. M.; Mottola, D. M.; Lovemberg, T. W;; Lewis, M. H.; Mailman, R. B. Trans-10,11-Dihydroxy-5,6,6a,7,8,12b-hexahydro[a]-phenanthridine: A Highly Potent Selective Dopamine Full Agonist. *J. Med. Chem.* **1990**, *33*, 1756−1764.
(6) Kaiser, C.; Dandridge, P. A.; Garvey, E.; Hahn, R. A.; Sarau, H. M.; Setler, P.E.; Bass, L. S.; Clardy, J. Absolute Stereochemistry and Dopaminergic Activity of Enantiomers of 2,3,4,5-Tetrahydro-7,8-dihydroxy-1-phenyl-1H-3-benzazepine. *J. Med. Chem.* **1982**, *25*, 697−703.
(7) Kebabian, J. W.; Michaelides, M. R.; Schoenleber, R. W. (Abbott Laboratories). Preparation of Phenanthridine Compounds as

Dopamine Agonists. PCT Int. Appl. WO 9204,356; *Annu. Drug Data Rep*. **1992**, *14*, 765.
(8) Knoerzer, T. A.; Nichols, D. E.; Brewster, W. K.; Watts, V. J.; Mottola, D.; Mailman, R. B. Dopaminergic Benzo[a]phenanthridine: Resolution and Pharmacological Evaluation of the Enantiomers of Dihydrexidine, the Full Efficacy D_1 Dopamine Receptor Agonist. *J. Med. Chem*. **1994**, *37*, 2453−2460.
(9) Civelli, O.; Bunzow, J. R.; Grandy, D. K.; Zhou, Q. Y.; Van Tol, H. H. M. Molecular Biology of the Dopamine Receptors. *Eur. J. Pharmacol. Mol. Pharmacol*. **1991**, *207*, 277−286.
(10) (a) Cannon, J. G. Dopamine Agonists: Structure-activity Relationships. In *Progress in Drug Research*; Jucker, E., Ed.; Birkhauser: Basel, 1985; Vol. 29, pp 303−414. (b) Gao, Y.; Ram, V. J.; Campbell, A.; Kula, N. S.; Baldessarini, R. J.; Neumeyer, J. L. Synthesis and Structural Requirements of N-Substituted Norapomorphines for Affinity and Activity at Dopamine D_1, D_2 and Agonist Receptor Sites in Rat Brain. *J. Med. Chem*. **1990**, *33*, 39−44.
(11) Weinstein, B. Condensation and Addition Reactions of 3-Phenylindene. *J. Org. Chem*. **1961**, *26*, 4161−4162.
(12) Rathke, M. W.; Inoue, N.; Varma, K. R.; Brown, H. C. A Stereospecific Synthesis of Alicyclic and Bicyclic Amines *via* Hydroboration. *J. Am. Chem. Soc.* **1966**, *88*, 2870−2871.
(13) Laus, G.; Tourwé, D.; Van Bist, G. Benzo- and Indoloquinolizidine derivatives XIX. The Synthesis and Pharmacological Activity of Some Quinolizidine Derivatives, Analogues of Butaclamol. *Heterocycles* **1984**, *22*, 311−331.
(14) Cannon, J. G.; Kirschbaum, S. K.; Amoo, V. E. D.; Johnson, A. K.; Long, J. P. 2,5-Dimethoxy Congeners of (+)- and (−)-3-(3-Hydroxyphenyl)-N-*n*-propylpiperidine. *J. Med. Chem*. **1993**, *36*, 2416−2419.
(15) Marchini, P.; Liso, G.; Reho, A.; Liberatore, F.; Micheletti Moracci, F. Sodium Borohydride-Carboxylic Acid Systems. Useful Reagents for the Alkylation of Amines. *J. Org. Chem*. **1975**, *40*, 3453−3456.
(16) Fujii, N.; Irie, H.; Yajima, H. Regioselective Cleavage of Aromatic Methyl Ethers by Methanesulphonic Acid in the Presence of Methionine. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2288−2289.
(17) Claudi, F.; Cingolani, G. M.; Giorgioni, G.; Cardellini, M.; Amenta, F.; Polidori, C. New 2-Pyridylethylamines with Dopaminergic Activity: Synthesis and Radioligand-binding Evaluation. *Eur. J. Med. Chem*. **1995**, *30*, 415−421.
(18) Gingrich, J. A.; Caron, M. G. Recent Advances in the Molecular Biology of Dopamine Receptors. *Annu. Rev. Neurosci.* **1993**, *16*, 299−321.
(19) Petterson, I.; Liljefors, T.; Bøgesø, K. Conformational Analysis and Structure-Activity Relationships of Selective Dopamine D-1 Receptor Agonists and Antagonists of the Benzazepine Series. *J. Med. Chem*. **1990**, *33*, 2197−2204.
(20) Brewster, W. K.; Nichols, D. E.; Watts, V. J.; Riggs, R. M.; Mottola, D.; Mailman, R. B. Evaluation of *cis*- and *trans*-9- and 11-Dihydroxy-5,6,6a,7,8,12b-hexahydro[a]phenanthridines as Structurally Rigid, Selective D_1 Dopamine Receptor Ligands. *J. Med. Chem*. **1995**, *38*, 318−327.
(21) McDermed, J. D.; Freeman H. S.; Ferris, R. M. Enantioselectivity in the Binding of (+) and (−)-2-Amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphtalene and Related Agonists to Dopamine Receptors. In *Catecholamines: Basic and Clinical Frontiers;* Usdin, E., Kopin, I. J., Barchas, J., Eds.; Pergamon Press: New York, 1979; Vol. 1, pp 568−570.
(22) Nichols, D. E. In *Dopamine Receptors;* Kaiser, C., Kebabian, J. W., Eds; ACS Symposium Series 224; American Chemical Society: Washington, DC, 1983; pp 201−218.
(23) Bertolini, G.; Vecchietti, V.; Mabilia, M.; Norcini, G.; Restelli, A.; Santangelo, F.; Villa, A. M.; Casagrande, C. Dopamine Receptor Agonists. I. Synthesis and Pharmacological Evaluation of 4-Aryl-substituted Analogues of 6,7-Dihydroxy-2-aminotetralin (6,7-ADTN) and Related Indane Compounds. *Eur. J. Med. Chem*. **1992**, *27*, 663−672.
(24) Molloy, A. G.; Waddington, J. L. Dopaminergic Behaviour Stereospecifically Promoted by the D-1 Agonist R-SK&F 38393 and Selectively Blocked by the D-1 AntagonistsSCH 23390. *Psychopharmacology* **1984**, *82*, 409−410.
(25) Starr, B. S.; Starr, M. S. Differential Effects of Dopamine D_1 and D_2 Agonists and Antagonists on Velocity of Movement, Rearing and Grooming in the Mouse. *Neuropharmacology* **1986**, *25*, 455−463.
(26) Ferrari, F.; Pelloni, F.; Giuliani, D. Behavioural Evidence that Different Neurochemical Mechanisms Underlie Stretching-yawning and Penile Erection Induced in Male Rats by SND 919, a new Selective D_2 Dopamine Receptor Agonist. *Psychopharmacology* **1993**, *113*, 172−176.
(27) Waddington, J. L.; Daly, S. A.; Downes, R. P.; Deveney, A. M.; McCauley, P. G.; O'Boyle, K. M. Behavioural Pharmacology of 'D-1-like' Dopamine Receptors: further Subtyping, New Pharmacological Probes and Interactions with 'D-2-like' Receptors *Prog. Neuro-Psychopharmacol. Biol. Psychiat*. **1995**, *19*, 811−831.
(28) Murray, A. M.; Waddington, J. L. New Putative Selective Agonists at the D-1 Dopamine Receptor: Behavioural and Neurochemical Comparison of CY 208−243 with SK&F 101384 and SK&F 103243. *Pharmacol. Biochem. Behav*. **1990**, *35*, 105−110.
(29) Gispen, W. H.; Wiegant, V. M.; Greven, H. M.; De Wied, D. Induction of Excessive Grooming in the Rat by Intraventricular Application of Peptides Derived from ACTH. Structure-Activity Studies. *Life Sc.* **1975**, *17*, 645−652.

JM960318V