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Il Farmaco 57 (2002) 303–313

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Synthesis and preliminary pharmacological evaluation of *trans*-2-amino-5(6)-chloro-6(5)-hydroxy-1-phenyl-2,3-dihydro-1*H*-indenes as dopamine receptor ligands

Antonio Di Stefano [a,*], Piera Sozio [a], Grazia Luisi [a], Ivana Cacciatore [a], Barbara Mosciatti [b], Barbara Costa [c], Antonio Lucacchini [c], Claudia Martini [c], Francesco Pinnen [a]

[a] *Dipartimento di Scienze del Farmaco, Università "G. D'Annunzio", Via dei Vestini 31, 66100 Chieti, Italy*
[b] *Dipartimento di Scienze Chimiche, Università di Camerino, Via S. Agostino 1, 62032 Camerino (MC), Italy*
[c] *Dipartimento di Psichiatria, Neurobiologia, Farmacologia e Biotecnologie, Università di Pisa, 56126 Pisa, Italy*

Received 22 October 2001; accepted 14 January 2002

Abstract

A series of *trans*-2-amino-5(6)-chloro-6(5)-hydroxy-1-phenyl-2,3-dihydro-1*H*-indenes were synthesized and evaluated for their binding affinity toward D_1-like and D_2-like dopamine (DA) receptors. The affinity and selectivity of these compounds were measured in a test involving displacement of [^{3}H]SCH 23390 or [^{3}H]YM-09-151-2, respectively, from homogenates of porcine striatal membranes. All tested compounds were poorly effective at DA receptors (K_i nM > 1000). The results suggest that introduction of chlorine substituent in five or six position of previously synthesized *trans*-2-amino-6(5)-hydroxy-1-phenyl-2,3-dihydro-1*H*-indenes decreases both D_1-like and D_2-like receptor affinity. © 2002 Éditions scientifiques et médicales Elsevier SAS. All rights reserved.

Keywords: N-substituted *trans*-2-amino-1-phenyl-2,3-dihydro-1*H*-indenes; Synthesis; Dopamine receptors; Binding affinity

1. Introduction

Dopamine-mediated neurotransmission plays a role in several psychiatric and neurological disorders and has been implicated in the action of many drugs of abuse [1]. Dopamine (DA) acts on the Central Nervous System (CNS) through a variety of receptors organized in two families called D_1-like and D_2-like, according to the nomenclature first proposed by Kebabian and Calne [2]. D_1-like (D_1 and D_5) and D_2-like (D_2, D_3, and D_4) all belong to the superfamily of G-protein receptors [3]. Most D_1-like selective agents belong to the phenyltetrahydrobenzazepine class like the prototypic D_1 selective antagonist SCH 23390 (**1**); its conformationally restricted analogue SCH 39166 (**2**) was proposed as a potential antipsychotic drug devoid of acute extrapyramidal side effects [4,5]. The pharmacological profile (agonistic or antagonistic properties) of these ligands critically depends upon the nature of substituents on the aromatic ring [6]. Furthermore, dopamine analogues containing a β-phenyl moiety show greater affinity for D_1-like receptors; the β-phenyl moiety is essential in conferring D_1 affinity and is also a major factor in selectivity of a drug for D_1-like receptors versus D_2-like receptors [7,8]. It was also noted that a halogen at the '*para*' position of the ethylamine side chain of β-phenyldopamines increased the D_1-like affinity of antagonists [9]. Among the tetrahydroben-

* Corresponding author. Tel.: +39-0871-3555338; fax: +39-0871-3555267.
E-mail address: adistefano@unich.it (A. Di Stefano).

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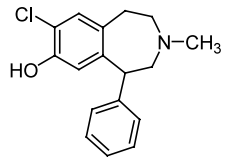
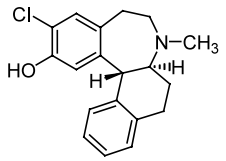
PII: S0014-827X(02)01206-5

zazepines, the 7-chloro substituent enhances D_1-like affinity and contributes to D_1-like antagonistic activity [10]. In an earlier work, Minor et al. showed that the *N*-methyl-6-chloro-7-hydroxy-1-phenyl-1,2,3,4,-tetrahydroisoquinoline (**3**) had significant affinity for the D_1-like receptor [11]. Previous work in this field led us to the discovery of a series of *trans*-2-amino-6(5)-hydroxy-1-phenyl-2,3-dihydro-1*H*-indenes which exhibited high and selective affinities for D_1-like receptors and contained the putative pharmacophore 2-phenyl-2-(3-hydroxyphenyl)ethylamine with a *trans* conformation [12]; in vivo studies indicated that these compounds cross the blood–brain barrier and exert a central agonistic activity. In order to further explore the structural basis of the affinity of the *trans*-2-amino-1-phenyl-2,3-dihydro-1*H*-indenes moiety, we describe here the synthesis of *trans*-2-amino-6-chloro-5-hydroxy-(or 5-chloro-6-hydroxy)-1-phenyl-2,3-dihydro-1*H*-indenes (**4a**, **5a**) as DA receptor ligands with potential selectivity toward D_1-like receptors. The new compounds were designed to investigate the significance of the halogen in the aromatic five or six positions of the *trans*-2-amino-6(5)-hydroxy-1-phenyl-2,3-dihydro-1*H*-indenes and to evaluate the variation of D_1-like and D_2-like binding site affinity.



1



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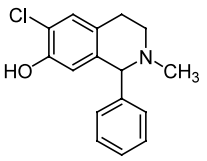

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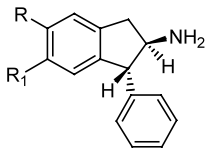


4a: R = OH; R_1 = Cl
5a: R = Cl; R_1 = OH

The amine was substituted with methyl, propyl, and allyl groups since they can modulate D_1-like and D_2-like receptor affinities.

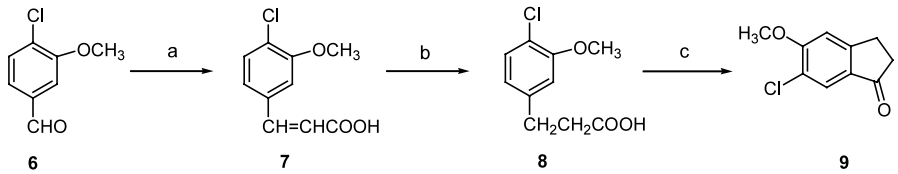
2. Chemistry

4-Chloro-3-methoxybenzaldehyde (**6**) was first prepared starting from 4-chloro-3-hydroxytoluene in four steps [13]. 6-Chloro-5-methoxyindan-1-one (**9**) was prepared from 4-substituted-3-methoxybenzaldehyde by the usual method as shown in Scheme 1 [14]. 5-Chloro-6-methoxyindan-1-one (**10**) was obtained from 3-chloro-4-methoxybenzaldehyde as previously described [15,16].

The new compounds were synthesized from 6-chloro-5-methoxy (or 5-chloro-6-methoxy)-3-phenyl-1*H*-indenes by reaction of 6-chloro-5-methoxy (or 5-chloro-6-methoxy)-indan-1-one (**9**, **10**) with phenylmagnesium bromide followed by stereospecific hydroboration; the reaction of organoboranes with hydroxylamine *O*-sulfonic acid yielded compounds **13** and **14** (see Scheme 2). The *trans* configuration was established on the basis of the *cis* addition mechanism of diborane and the ^{1}H NMR data (coupling constant of 7.93 Hz for the hydrogens at the one- and two-positions) [17]. The di-*n*-propyl derivatives were obtained by alkylation of the bases **13**, **14** with the $NaBH_4$–propionic acid complex [18]. The *N*-*n*-propyl-*N*-methyl and *N*-allyl-*N*-methyl derivatives were prepared as outlined in Scheme 3. The amines **4a**–**d**, **5a**–**d** were demethylated by refluxing with HBr–CH_3COOH 1:1. Cleavage of the methoxyl groups of the derivatives **4e**, **4f**, **5e**, **5f** was achieved by employing the methionine–methanesulfonic acid procedure [19]. The hydroxy derivatives **4a**–**f**, **5a**–**f** are listed in Table 1.

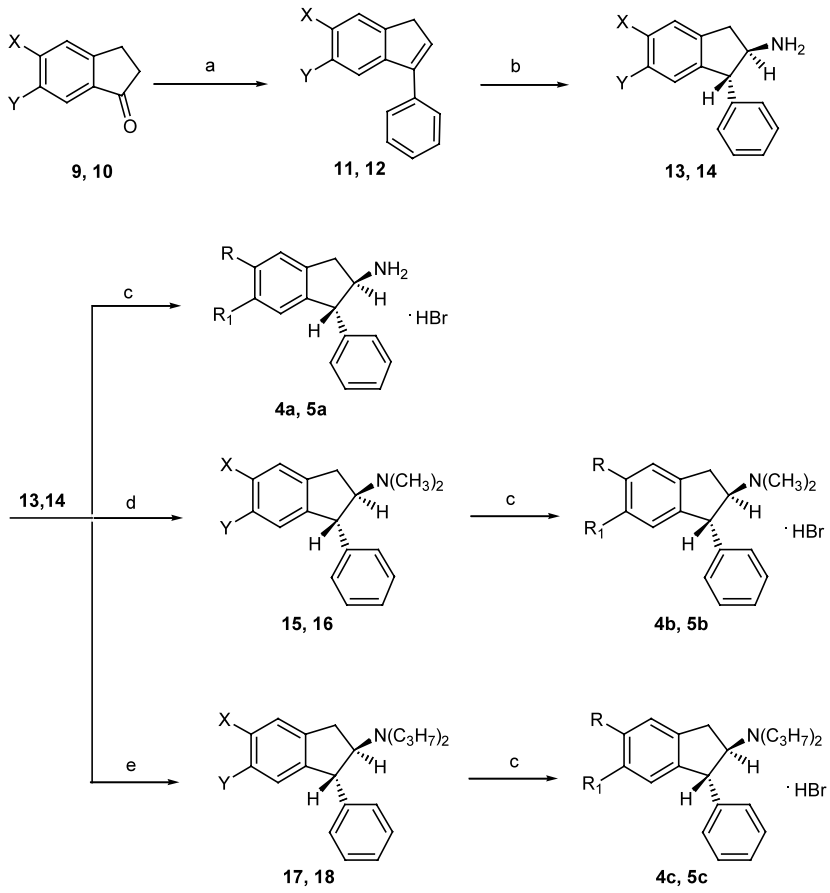
3. Experimental

Melting points (m.p.) were determined on a Buchi B-540 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 300-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 FTIR 1600 spectrometer as Nujol mulls or liquid films. The identity of all new compounds was confirmed both by elemental analysis and NMR data; homogeneity was confirmed by TLC on silica gel Merck 60 F254. Solutions were routinely dried over anhydrous sodium sulfate prior to



6 **7** **8** **9**

Scheme 1. Synthetic pathway of compound **9**. Reagents: (a) malonic acid, piperidine, pyiridine; (b) H_2, PtO_2, anhydrous MeOH; (c) $SOCl_2$, $AlCl_3$, CS_2.



9, 11, 13, 15, 17: X=OCH_3; Y=Cl **10, 12, 14, 16, 18**: X=Cl; Y=OCH_3 **4 a-c**: R=OH; R_1=Cl **5 a-c**: R=Cl; R_1=OH

Scheme 2. Reagents: (a) C_6H_5MgBr, anhydrous Et_2O, anhydrous THF; (b) $NaBH_4$–BF_3, H_2NOSO_3H, diglyme; (c) CH_3COOH–HBr 48%; (d) HCOOH, HCHO 38%; (e) C_2H_5COOH, $NaBH_4$, anhydrous benzene.

evaporation. Chromatographic purifications were performed by Merck 60 70-230 mesh ASTM silica gel columns from Merck with the reported solvent.

3.1. trans 4-chloro-3-Methoxycinnamic acid (7)

To the 4-chloro-3-methoxybenzaldehyde (**6**) (17.0 g, 0.1 mol) malonic acid (20.8 g, 0.2 mol) and pyridine (40 ml) were added. The malonic acid was dissolved by stirring and warming in a steam bath. Piperidine (1.5 ml) was then added and the mixture was heated to 80 °C for 1 h. The material was finally heated under reflux (109–115 °C) for an additional 3 h.

After being cooled, the reaction mixture was poured into a large beaker with 400 ml of cold water. The mixture was then acidified with concentrated HCl. The white crystals were separated by suction filtration and purified by recrystallization from methyl ethyl ketone: m.p. 117–119 °C; yield 76%; ^{1}H NMR (DMSO-d_6): δ 12.44 (s, 1H, OH), 7.56 (d, 1H, $J = 16.12$ Hz, –CH=), 7.50–7.22 (m, 3H, ArH), 6.64 (d, 1H, Ar–CH=), 3.96 (s, 3H, OCH_3).

3.2. 3-(4-chloro-3-methoxy)phenyl-propanoic acid (8)

A solution of **7** (4.24 g, 20 mmol) in 120 ml of anhydrous CH_3OH was hydrogenated at room temperature (r.t.) over PtO_2 hydrate (0.7 g) at 1 bar for 6 h. The catalyst was removed by filtration through Celite, and the solvent was removed by rotary evaporation to yield a white solid, which was recrystallized from Et_2O: m.p. 113–115 °C; yield 72%; IR ν_{max} (KBr): 1715 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 11.00 (s, 1H, OH), 7.27 (m, 1H, ArH), 6.80 (m, 2H, ArH), 3.92 (s, 3H, OCH_3), 2.95 (t, 2H, $J = 7.63$ Hz, CH_2–CO), 2.69 (t, 2H, CH_2Ar).

3.3. 6-Chloro-5-methoxyindan-1-one (9)

The mixture of propanoic acid **8** (4.28 g, 20 mmol) and thionyl chloride (3.2 g, 27 mmol) was heated at

60 °C for 40 min. The excess thionyl chloride was removed with a water pump and then the oily residue was cooled. Carbon disulfide (17.5 ml) and $AlCl_3$ (3 g, 23 mmol) were added and the reaction mixture was stirred at r.t. for 1 h. After this time, the cold hydrochloric acid was added and the product was extracted with AcOEt. The organic phase was dried and filtered, and the residue was recrystallized from AcOEt–*n*-hexane: m.p. 130–132 °C; yield 60%; ^{1}H NMR ($CDCl_3$): δ 7.70 (m, 1H, ArH), 6.93 (m, 1H, ArH), 3.92 (s, 3H, OCH_3), 3.05 (t, 2H, $J = 5.86$ Hz, CH_2–CO), 2.65 (t, 2H, CH_2Ar).

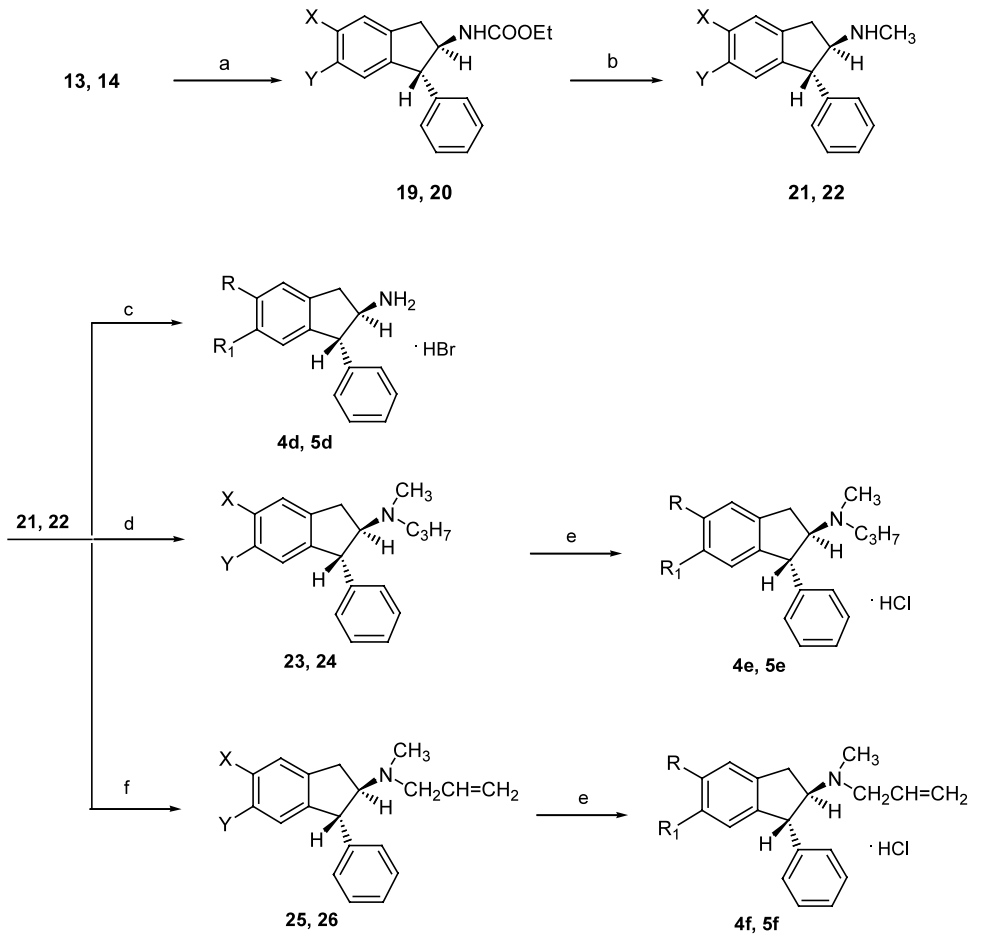
3.4. 6-Chloro-5-methoxy-1-phenyl-1H-indene (**11**)

To the magnetically stirred suspension of 0.97 g (40 mmol) of magnesium, 1 crystal of iodine and 20 ml of anhydrous Et_2O, 5 ml of a solution of bromobenzene were added, obtained from 6.34 g (40 mmol) of bromobenzene in 100 ml of anhydrous Et_2O. The solution became muddy by heating, then the remaining solution of bromobenzene was added dropwise at r.t. The reaction mixture was refluxed for 3 h.

After cooling, a solution of **9** (5.9 g, 30 mmol) was added in 45 ml of anhydrous THF. The reaction mixture was refluxed overnight. After cooling, 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 HCl 2 N and extracted with Et_2O. The organic solution was dried and filtered; after removal of the solvent a product was obtained which was purified by column chromatography with cyclohexane–AcOEt 9.5:0.5 as eluent; R_f: 0.34; m.p. 82–84 °C; yield: 70%; ^{1}H NMR ($CDCl_3$): δ 7.60–7.25 (m, 6H, ArH), 7.18 (m, 1H, ArH), 6.49 (t, 1H, $J = 2.05$ Hz, =CH–), 3.95 (s, 3H, OCH_3), 3.48 (d, 2H, CH_2).

3.5. 5-Chloro-6-methoxy-1-phenyl-1H-indene (**12**)

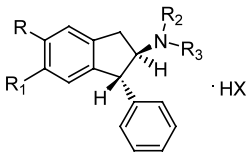
Compound **12** was prepared from **10** (5.9 g, 30 mmol) according to the procedure described for the synthesis of **11**.



19, 21, 23, 25: X=OCH_3; Y=Cl **20, 22, 24, 26**: X=Cl; Y=OCH_3 **4 d-f**: R=OH; R'=Cl **5 d-f**: R=Cl; R'=OH

Scheme 3. Reagents: (a) $ClCOOC_2H_5$, Et_3N, anhydrous Et_2O; (b) $LiAlH_4$, anhydrous Et_2O; (c) CH_3COOH–HBr 48%; (d) *n*-C_3H_7I, K_2CO_3, acetone; (e) CH_3SO_3H, methionine, HCl; (f) CH_2=CH–CH_2Br, K_2CO_3, EtOH abs.

Table 1
Inhibition of [^{3}H]SCH 23390 (D_1-like) and [^{3}H]YM-09-151-2 (D_2-like) binding to porcine striatal membranes of *trans*-2-amino-6-chloro-5-hydroxy-(or 5-chloro-6-hydroxy)-1-phenyl-2,3-dihydro-1*H*-indenes **4a–f** and **5 a–f**



Compound	R	R_1	R_2	R_3	X	K_i (μM) [a]	
						D_1-like	D_2-like
4a	OH	Cl	H	H	Br	4.25 ± 0.31	3.80 ± 0.30
4b	OH	Cl	CH_3	CH_3	Br	1.88 ± 0.18	1.50 ± 0.13
4c	OH	Cl	*n*-C_3H_7	*n*-C_3H_7	Br	5.50 ± 0.43	4.50 ± 0.33
4d	OH	Cl	H	CH_3	Br	4.24 ± 0.35	5.00 ± 0.41
4e	OH	Cl	*n*-C_3H_7	CH_3	Cl	4.20 ± 0.36	2.50 ± 0.23
4f	OH	Cl	CH_2CHCH_2	CH_3	Cl	6.05 ± 0.51	4.20 ± 0.35
5a	Cl	OH	H	H	Br	3.25 ± 0.25	3.50 ± 0.28
5b	Cl	OH	CH_3	CH_3	Br	1.75 ± 0.19	1.50 ± 0.14
5c	Cl	OH	*n*-C_3H_7	*n*-C_3H_7	Br	3.00 ± 0.29	1.77 ± 0.16
5d	Cl	OH	H	CH_3	Br	1.76 ± 0.19	2.25 ± 0.20
5e	Cl	OH	*n*-C_3H_7	CH_3	Cl	5.50 ± 0.41	2.70 ± 0.22
5f	Cl	OH	CH_2CHCH_2	CH_3	Cl	3.25 ± 0.31	2.10 ± 0.19
Dopamine						2.56 ± 0.14	3.53 ± 0.43
SCH 23390						$8.3 \times 10^{-3} \pm 0.7 \times 10^{-3}$	NT [b]
Quinpirole						NT	1.2 ± 0.11

[a] The K_i values are mean ± SEM of at least three experiments.
[b] NT = not tested.

R_f: 0.61; m.p. 84–86 °C; yield 75%; ^{1}H NMR ($CDCl_3$): δ 7.60–7.30 (m, 6H, ArH), 7.14 (m, 1H, ArH), 6.58 (t, 1H, $J = 2.35$ Hz, =CH–), 3.92 (s, 3H, OCH_3), 3.45 (d, 2H, CH_2).

3.6. *trans*-2-Amino-6-chloro-5-methoxy-1-phenyl-2,3-dihydro-1H-indene (**13**)

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 6.4 g (25 mmol) of **11**. The flask was immersed in an ice–water bath and $BF_3 \cdot Et_2O$ (1.95 g, 13.75 mmol) was added dropwise. The solution was then stirred at r.t. 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 then cooled, treated with 10 ml of concentrated HCl and poured into 100 ml of water. The acidic aqueous phase was extracted with Et_2O to remove diglyme and residual boric acid. The solution was then made strongly alkaline with NaOH 2 N 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; yield 35%; ^{1}H NMR ($CDCl_3$): δ 7.45–7.18 (m, 5H, ArH), 6.89 (m, 1H, ArH), 6.76 (m, 1H, ArH), 3.94 (s, 3H, OCH_3), 3.85 (d, 1H, $J = 7.50$ Hz, CH–C), 3.65 (m, 1H, CH–N), 3.25 (dd, 1H, $J_1 = 15.25$ Hz, $J_2 = 7.04$ Hz, CH_2), 2.75 (dd, 1H, $J_1 = 15.25$ Hz, $J_2 = 9.38$ Hz, CH_2), 2.10 (bs, 2H, NH_2).

3.7. *trans*-2-Amino-5-chloro-6-methoxy-1-phenyl-2,3-dihydro-1H-indene (**14**)

Compound **14** was prepared from **12** (6.4 g, 25 mmol) according to the procedure described for the synthesis of **13**.

R_f: 0.4; yield: 33%; ^{1}H NMR ($CDCl_3$): δ 7.25–7.06 (m, 5H, ArH), 6.47 (m, 1H, ArH), 6.35 (m, 1H, ArH), 3.89 (s, 3H, OCH_3), 3.72 (d, 1H, $J = 7.46$ Hz, CH–C), 3.54 (m, 1H, CH–N), 3.07 (dd, 1H, $J_1 = 15.07$ Hz, $J_2 = 7.02$ Hz, CH_2), 2.69 (dd, 1H, $J_1 = 15.07$ Hz, $J_2 = 9.17$ Hz, CH_2), 2.08 (bs, 2H, NH_2).

3.8. *trans*-2-Amino-6-chloro-5-hydroxy-1-phenyl-2,3 dihydro-1H-indene hydrobromide (**4a**)

A stirred solution of the methoxylated amine **13** (1.4 g, 5 mmol), acetic acid (10 ml) and freshly distilled 48% HBr (10 ml) was refluxed for 4 h, and evaporated in vacuo; the residue was dissolved in absolute EtOH and evaporated in vacuo. The product was recrystallized from AcOEt–Et_2O.

M.p. 220–222 °C; yield: 97%; IR ν_{max} (KBr): 3438 (OH), 3046 (NH_3^+) cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.20 (s, 1H, OH), 8.25 (bs, 3H, NH_3^+), 7.50–7.20 (m, 5H, ArH), 6.95 (m, 1H, ArH), 6.80 (m, 1H, ArH), 4.33 (d, 1H, $J = 7.50$ Hz, CH–C), 3.95 (m, 1H, CH–N), 3.25 (dd, 1H, $J_1 = 16.25$ Hz, $J_2 = 6.88$ Hz, CH_2), 2.91 (dd, 1H, $J_1 = 16.25$ Hz. $J_2 = 7.03$ Hz, CH_2).

3.9. trans-2-Amino-5-chloro-6-hydroxy-1-phenyl-2,3-dihydro-1H-indene hydrobromide (**5a**)

Compound **5a** was prepared from **14** (1.4 g, 5 mmol) according to the procedure described for the synthesis of **4a**.

M.p. 298–300 °C; yield: 97%; IR ν_{max} (KBr): 3429 (OH), 3020 (NH_3^+) cm^{-1}; ^1H NMR (DMSO-d_6): δ 9.95 (s, 1H, OH), 8.23 (bs, 3H, NH_3^+), 7.45–7.15 (m, 6H, ArH), 6.40 (m, 1H, ArH), 4.33 (d, 1H, $J = 7.87$ Hz, CH–C), 3.95 (m, 1H, CH–N), 3.31 (dd, 1H, $J_1 = 14.75$ Hz, $J_2 = 7.18$ Hz, CH_2), 2.87 (dd, 1H, $J_1 = 14.75$ Hz, $J_2 = 7.50$ Hz, CH_2).

3.10. trans-N,N-Dimethyl-2-amino-6-chloro-5-methoxy-1-phenyl-2,3-dihydro-1H-indene (**15**)

A suspension of methoxylated amine **13** (0.8 g, 3 mmol) in 12 ml of 95% formic acid and 8 ml of 38% formaldehyde was stirred at reflux for 4, 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 in vacuo to afford a crude product which was purified by column chromatography with $CHCl_3$–CH_3OH 6:1 as eluent.

R_f: 0.77; yield: 95%; ^1H NMR ($CDCl_3$): δ 7.38–7.15 (m, 5H, ArH), 6.83 (m, 1H, ArH), 6.77 (m, 1H, ArH), 4.27 (d, 1H, $J = 7.04$ Hz, CH–C), 3.90 (s, 3H, OCH_3), 3.47 (m, 1H, CH–N), 3.18 (dd, 1H, $J_1 = 16.12$ Hz, $J_2 = 7.62$ Hz, CH_2), 3.15 (dd, 1H, $J_1 = 16.12$ Hz, $J_2 = 7.28$ Hz, CH_2), 2.24 (s, 6H, CH_3).

3.11. trans-N,N-Dimethyl-2-amino-6-chloro-5-hydroxy-1-phenyl-2,3-dihydro-1H-indene hydrobromide (**4b**)

The methoxylated dimethylamine **15** was converted into **4b** according to the procedure described for the synthesis of **4a**.

M.p. 211–213 °C; yield: 83%; ^1H NMR (DMSO-d_6): δ 10.23 (s, 1H, OH), 10.03 (bs, 1H, NH^+), 7.48–7.20 (m, 5H, ArH), 6.96 (m, 1H, ArH), 6.68 (m, 1H, ArH), 4.70, (d, 1H, $J = 4.44$ Hz, CH–C), 4.32 (m, 1H, CH–N), 3.42 (dd, 1H, $J_1 = 15.50$ Hz, $J_2 = 7.99$ Hz, CH_2), 3.22 (dd, 1H, $J_1 = 15.50$ Hz, $J_2 = 6.00$ Hz, CH_2), 2.92 and 2.60 (two d, 6H, $2CH_3$).

3.12. trans-N,N-Dimethyl-2-amino-5-chloro-6-methoxy-1-phenyl-2,3-dihydro-1H-indene (**16**)

Compound **16** was prepared from **14** (0.8 g, 3 mmol) according to the procedure described for the synthesis of **15**.

R_f: 0.77; yield: 86%; ^1H NMR ($CDCl_3$): δ 7.50–7.20 (m, 6H, ArH), 6.53 (m, 1H, ArH), 4.78 (d, 1H, $J = 4.39$ Hz, CH–C), 4.30 (m, 1H, CH–N), 3.66 (s, 3H, OCH_3), 3.37 (dd, 1H, $J_1 = 16.50$ Hz, $J_2 = 7.30$ Hz, CH_2), 3.15 (dd, 1H, $J_1 = 16.50$ Hz, $J_2 = 4.62$ Hz, CH_2), 2.63 (s, 6H, CH_3).

3.13. trans-N,N-Dimethyl-2-amino-5-chloro-6-hydroxy-1-phenyl-2,3-dihydro-1H-indene hydrobromide (**5b**)

Compound **5b** was prepared from **16** according to the procedure described for the synthesis of **4a**.

M.p. 187–189 °C; yield: 85%; IR ν_{max} (KBr): 3409 (OH), 3159 (NH^+) cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.26 (s, 1H, OH), 10.00 (bs, 1H, NH^+), 7.45–7.20 (m, 6H, ArH), 6.34 (m, 1H, ArH), 4.69, (d, 1H, $J = 5.88$ Hz, CH–C), 4.31 (m, 1H, CH–N), 3.35 (dd, 1H, $J_1 = 17.60$ Hz, $J_2 = 7.12$ Hz, CH_2), 3.19 (dd, 1H, $J_1 = 17.60$ Hz, $J_2 = 7.05$ Hz, CH_2), 2.82 and 2.60 (two d, 6H, CH_3).

3.14. trans-N,N-di-n-Propyl-2-amino-6-chloro-5-methoxy-1-phenyl-2,3-dihydro-1H-indene (**17**)

To the magnetically stirred solution of amine **13** (2.3 g, 8.4 mmol) in anhydrous benzene (40 ml) sodium borohydride (3.15 g, 84 mmol) was added and then propionic acid (10.4 g, 140 mmol). The mixture was refluxed for 3 h and after cooling was basified with NaOH 2 N. The organic phase was evaporated and the oily residue purified by column chromatography with $CHCl_3$–CH_3OH 6:1 as eluent.

R_f: 0.48; yield: 71%; ^1H NMR ($CDCl_3$): δ 7.40–7.18 (m, 5H, ArH), 6.84 (m, 2H, ArH), 4.09 (d, 1H, $J = 4.69$ Hz, CH–C), 3.90 (s, 3H, OCH_3), 3.78 (m, 1H, CH–N), 3.55 (dd, 1H, $J_1 = 16.40$ Hz, $J_2 = 7.15$ Hz, CH_2), 2.80 (dd, 1H, $J_1 = 16.40$ Hz, $J_2 = 4.51$ Hz, CH_2), 2.56 (m, 4H, N–CH_2–C), 1.46 (m, 4H, N–C–CH_2–C), 0.85 (s, 6H, CH_3).

3.15. trans-N,N-di-n-Propyl-2-amino-6-chloro-5-hydroxy-1-phenyl-2,3-dihydro-1H-indene hydrobromide (**4c**)

The methoxylated dipropylamine **17** was converted into hydroxylated **4c** according to the procedure described for the synthesis of **4a**.

M.p. 216–218 °C; yield: 70%; IR ν_{max} (KBr): 3382 (OH), 3162 (NH^+) cm^{-1}; ^1H NMR (DMSO-d_6): δ

10.18 (s, 1H, OH), 8.90 (bs, 1H, NH^+), 7.40–7.18 (m, 5H, ArH), 6.90 (m 1H, ArH), 6.72 (m 1H, ArH), 4.44 (d, 1H, $J = 6.10$ Hz, CH–C), 4.12 (m, 1H, CH–N), 3.22 (dd, 1H, $J_1 = 14.69$ Hz, $J_2 = 7.10$ Hz, CH_2), 3.06 (dd, 1H, $J_1 = 14.69$ Hz, $J_2 = 6.12$ Hz, CH_2), 2.84 (m, 4H, 2N–CH_2–C), 1.70 and 1.22 (two m, 4H, N–C–CH_2–C), 1.07 and 0.82 (two t, 6H, N–C–C–CH_3).

3.16. trans-N,N-di-n-Propyl-2-amino-5-chloro-6-methoxy-1-phenyl-2,3-dihydro-1H-indene (18)

Compound **18** was prepared from **14** (2.3 g, 8.4 mmol) according to the procedure described for the synthesis of **17**.

R_f: 0.52; yield: 86%; ^{1}H NMR ($CDCl_3$): δ 7.45–7.25 (m, 6H, ArH), 6.35 (m, 1H, ArH), 4.80 (m, 1H, CH–N),4.44 (d, 1H, $J = 4.39$ Hz, CH–C), 3.68 (s, 3H, OCH_3), 3.42 (dd, 1H, $J_1 = 16.50$ Hz, $J_2 = 7.30$ Hz, CH_2), 3.30 (dd, 1H, $J_1 = 16.50$ Hz, $J_2 = 4.62$ Hz, CH_2), 2.98 (m, 4H, N–CH_2–C), 1.47 (m, 4H, N–C–CH_2–C), 0.67 (s, 6H, CH_3).

3.17. trans-N,N-di-n-Propyl-2-amino-5-chloro-6-hydroxy-1-phenyl-2,3-dihydro-1H-indene hydrobromide (5c)

Compound **5c** was prepared from **18** according to the procedure described for the synthesis of **4a**.

M.p. 244–246 °C; yield: 83%; IR ν_{max} (KBr): 3355 (OH), 3156 (NH^+) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 9.97 (s, 1H, OH), 9.88 (bs, 1H, NH^+), 7.45–7.25 (m, 6H, ArH), 6.24 (m, 1H, ArH), 4.71 (d, 1H, $J = 7.34$ Hz, CH–C), 4.51 (m, 1H, CH–N), 3.40 (dd, 1H, $J_1 = 16.46$ Hz, $J_2 = 7.28$ Hz, CH_2), 3.25 (dd, 1H, $J_1 = 16.46$ Hz, $J_2 = 6.12$ Hz, CH_2), 2.98 (m, 4H, 2N–CH_2–C), 1.70 and 1.24 (two m, 4H, N–C–CH_2–C), 0.90 and 0.45 (two t, 6H, N–C–C–CH_3).

3.18. trans-6-Chloro-5-methoxy-1-phenyl-2-[(ethoxycarbonyl)amino]-2,3-dihydro-1H-indene (19)

A solution of ethyl chloroformate (1.18 g, 11 mmol) in anhydrous Et_2O (15 ml) was added dropwise to a solution of amine **13** (3 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 r.t. and then 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; m.p. 121–123 °C; yield 80%; IR ν_{max} (KBr): 3310 (NH), 1675 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.38–7.10 (m, 5H, ArH), 6.92 (m, 1H, ArH), 6.84 (m, 1H, ArH), 4.92 (bs, 1H, NH), 4.36 (m, 1H, CH–N), 4.16 (m, 2H, OCH_2), 4.08 (d, 1H, $J = 7.14$ Hz CH–C), 3.92 (s, 3H, OCH_3), 3.60 (dd, 1H, $J_1 = 16.32$ Hz, $J_2 = 7.08$ Hz, CH_2), 2.78 (dd, 1H, $J_1 = 16.32$ Hz, $J_2 = 5.71$ Hz, CH_2), 1.22 (t, 3H, CH_3).

3.19. trans-5-Chloro-6-methoxy-1-phenyl-2-[(ethoxycarbonyl)amino]-2,3-dihydro-1H-indene (20)

Compound **20** was prepared from **14** (3 g, 11 mmol) according to the procedure described for the synthesis of **19**.

M.p. 128–129 °C; yield: 87%; IR ν_{max} (KBr): 3337 (NH), 1650 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.38–7.18 (m, 6H, ArH), 6.49 (m, 1H, ArH), 5.02 (bs, 1H, NH), 4.23 (d, 1H, $J = 6.86$ Hz, CH–C), 4.12 (m, 1H, CH–N), 3.90 (m, 2H, OCH_2), 3.64 (s, 3H, OCH_3), 3.17 (dd, 1H, $J_1 = 17.14$ Hz, $J_2 = 8.57$ Hz, CH_2), 2.70 (dd, 1H, $J_1 = 17.14$ Hz, $J_2 = 6.43$ Hz, CH_2), 1.09 (t, 3H, $J = 6.08$ Hz, CH_3).

3.20. trans-6-Chloro-5-methoxy-2-(methylamino)-1-phenyl-2,3-dihydro-1H-indene (21)

A solution of **19** (3.3 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. The oily residue was purified by column chromatography with $CHCl_3$–CH_3OH 6:1 as eluent.

R_f: 0.54; yield: 48%; ^{1}H NMR ($CDCl_3$): δ 7.40–7.18 (m, 5H, ArH), 6.83 (m, 1H, ArH), 6.77 (m, 1H, ArH), 4.06 (d, 1H, $J = 8.57$ Hz, CH–C), 3.77 (s, 3H, OCH_3), 3.43 (m, 1H, CH–N), 3.26 (dd, 1H, $J_1 = 15.42$ Hz, $J_2 = 7.71$ Hz, CH_2), 2.77 (dd, 1H, $J_1 = 15.42$ Hz, $J_2 = 6.43$ Hz, CH_2), 2.40 (s, 3H, CH_3), 2.00 (bs, 1H, NH).

3.21. trans-5-Chloro-6-methoxy-2-(methylamino)-1-phenyl-2,3-dihydro-1H-indene (22)

Compound **22** was prepared from **20** (3.3 g, 9.6 mmol) according to the procedure described for the synthesis of **21**.

R_f: 0.44; yield: 73%; ^{1}H NMR ($CDCl_3$): δ 7.38–7.15 (m, 6H, ArH), 6.42 (m, 1H, ArH), 4.07, (d, 1H, $J =$ 7.62 Hz, CH–C), 3.71 (s, 3H, OCH_3), 3.43 (m, 1H, CH–N), 3.20 (dd, 1H, $J_1 = 15.05$ Hz, $J_2 = 6.74$ Hz, CH_2), 2.70 (dd, 1H, $J_1 = 15.05$ Hz, $J_2 = 7.62$ Hz, CH_2), 2.40 (s, 3H, CH_3); 2.20 (bs, 1H, NH).

3.22. trans-6-Chloro-5-hydroxy-2-(methylamino)-1-phenyl-2,3-dihydro-1H-indene Hydrobromide (4d)

Compound **4d** was prepared from **21** (1.4 g, 5 mmol) according to the procedure described for the synthesis of **4a**.

M.p. 251–253 °C; yield: 92%; IR ν_{max} (KBr): 3237 (OH), 3023 (NH_2^+) cm^{-1}; ^1H NMR (DMSO-d_6): δ 9.37 (s, 1H, OH), 8.92 (bs, 2H, NH_2^+), 7.38–7.18 (m, 5H, ArH), 6.71 (m, 1H, ArH), 6.59 (m, 1H, ArH), 4.41 (d, 1H, $J = 6.10$ Hz, CH–C), 3.97 (m, 1H, CH–N), 3.36 (dd, 1H, $J_1 = 17.29$ Hz, $J_2 = 6.12$ Hz, CH_2), 3.17 (dd, 1H, $J_1 = 17.29$ Hz, $J_2 = 5.71$ Hz, CH_2), 2.54 (t, 3H, CH_3).

3.23. trans-5-Chloro-6-hydroxy-2-(methylamino)-1-phenyl-2,3-dihydro-1H-indene hydrobromide (**5d**)

Compound **5d** was prepared from **22** (1.4 g, 5 mmol) according to the procedure described for the synthesis of **4a**.

M.p. 243–245 °C; yield: 98%; IR ν_{max} (KBr): 3228 (OH), 2986 (NH_2^+) cm^{-1}; ^1H NMR (DMSO-d_6): δ 9.98 (s, 1H, OH), 8.96 (bs, 2H, NH_2^+), 7.36–7.18 (m, 6H, ArH), 6.38 (m 1H, ArH), 4.44 (d, 1H, $J = 6.45$ Hz, CH–C), 4.00 (m, 1H, CH–N), 3.36 (dd, 1H, $J_1 = 16.10$ Hz, $J_2 = 6.85$ Hz, CH_2), 2.70 (dd, 1H, $J_1 = 16.10$ Hz, $J_2 = 6.14$ Hz, CH_2), 2.51 (t, 3H, CH_3).

3.24. trans-N-Methyl-N-n-propyl-2-amino-6-chloro-5-methoxy-1-phenyl-2,3-dihydro-1H-indene (**23**)

A mixture of amine **21** (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 the solvent in vacuo, water was added and the mixture 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. The desired fraction was collected and evaporated.

R_f: 0.48; yield: 71%; ^1H NMR ($CDCl_3$): δ 7.36–7.08 (m, 5H, ArH), 6.82 (m, 1H, ArH), 6.70 (m, 1H, ArH), 4.30 (d, 1H, $J = 4.38$ Hz, CH–C), 3.88 (s, 3H, OCH_3), 3.62 (m, 1H, CH–N), 3.18 (dd, 1H, $J_1 = 15.70$ Hz, $J_2 = 6.14$ Hz, CH_2), 2.92 (dd, 1H, $J_1 = 15.70$ Hz, $J_2 = 4.32$ Hz, CH_2), 2.40 (m, 2H, N–CH_2–C), 2.24 (s, 3H, CH_3), 1.42 (m, 2H, N–C–CH_2–C), 0.78 (t, 3H, N–C–C–CH_3).

3.25. trans-N-Methyl-N-n-propyl-2-amino-6-chloro-5-hydroxy-1-phenyl-2,3-dihydro-1H-indene hydrochloride (**4e**)

To the product **23** (1.55 g, 4.7 mmol) water (3.6 ml), methanesulfonic acid (57 ml) and methionine (7.9 g, 53.2 mmol) were added. 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. It was then extracted with AcOEt. The organic extracts, washed with aqueous $NaHSO_3$ and water, were dried and evaporated. The residue was dissolved in Et_2O, and HCl gas was bubbled. The salt was recovered and dried.

M.p. 98–100 °C; yield: 60%; IR ν_{max} (KBr): 3208 (OH), 2973 (NH^+) cm^{-1}; ^1H NMR (DMSO-d_6): δ 8.60 (bs, 2H, NH^+ e OH), 7.40–7.22 (m, 5H, ArH), 6.90 (m, 1H, ArH), 6.78 (m, 1H, ArH), 4.80 (m, 1H, CH–N), 4.24 (d, 1H, $J = 4.40$ Hz, CH–C), 3.42 (dd, 1H, $J_1 = 15.32$ Hz, $J_2 = 6.46$ Hz, CH_2), 2.92 (dd, 1H, $J_1 = 15.32$ Hz, $J_2 = 4.53$ Hz, CH_2), 2.53 (m, 2H, N–CH_2–C), 2.11 and 2.02 (two s, 3H, N–CH_3), 1.65 and 1.42 (two m, 2H, N–C–CH_2), 0.80 and 0.52 (two t, 3H, N–C–C–CH_3).

3.26. trans-N-Methyl-N-n-propyl-2-amino-5-chloro-6-methoxy-1-phenyl-2,3-dihydro-1H-indene (**24**)

Compound **24** was prepared from **22** (1.5 g, 5.2 mmol) according to the procedure described for the synthesis of **23**.

R_f: 0.27; yield: 90%; ^1H NMR ($CDCl_3$): δ 7.42–7.10 (m, 5H, ArH), 6.48 (m, 1H, ArH), 4.40 (d, 1H, $J = 6.23$ Hz, CH–C), 3.79 (s, 3H, OCH_3), 3.62 (m, 1H, CH–N), 3.19 (dd, 1H, $J_1 = 15.93$ Hz, $J_2 = 8.24$ Hz, CH_2), 2.98 (dd, 1H, $J_1 = 15.93$ Hz, $J_2 = 6.76$ Hz, CH_2), 2.44 (m, 2H, N–CH_2–C), 2.30 (s, 3H, CH_3), 1.50 (m, 2H, N–C–CH_2–C), 0.87 (t, 3H, N–C–C–CH_3).

3.27. trans-N-Methyl-N-n-propyl-2-amino-5-chloro-6-hydroxy-1-phenyl-2,3-dihydro-1H-indene hydrochloride (**5e**)

Compound **5e** was prepared from **24** (1.5 g, 5.2 mmol) according to the procedure described for the synthesis of **4e**.

M.p. 117–119 °C; yield: 65%; IR ν_{max} (KBr): 3194 (OH), 2953 (NH^+) cm^{-1}. ^1H NMR (DMSO-d_6): δ 8.70–8.45 (bs, 2H, NH^+ e OH), 7.38–7.20 (m, 6H, ArH), 6.50 (m, 1H, ArH), 4.88 (d, 1H, $J = 7.83$, CH–C), 4.25 (m, 1H, CH–N), 3.40 (dd, 1H, $J_1 = 14.06$ Hz, $J_2 = 7.03$ Hz, CH_2), 3.20 (dd, 1H, $J_1 = 14.06$ Hz, $J_2 = 5.58$ Hz, CH_2), 2.89 (m, 2H, N–CH_2–C), 2.62 and 2.56 (two s, 3H, N–CH_3), 1.70 and 1.32 (two m, 2H, N–C–CH_2–C), 0.88 and 0.54 (two t, 3H, $J = 7.03$, N–C–C–CH_3).

3.28. trans-N-Methyl-N-allyl-2-amino-6-chloro-5-hydroxy-1-phenyl-2,3-dihydro-1H-indene hydrochloride (**25**)

A mixture of amine **21** (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 3H. After removal of the solvent in vacuo, water was added and the mixture 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.

R_f: 0.56; yield: 60%; ^{1}H NMR ($CDCl_3$): δ 7.38–7.16 (m, 5H, ArH), 6.79 (s, 1H, ArH), 6.70 (s, 1H, ArH), 5.76 (m, 1H, N–C–CH=), 5.06 (m, 2H, N–C–C=CH_2), 4.30 (d, 1H, $J = 4.70$ Hz, CH–C), 4.12 (m, 1H, CH–N), 3.78 (s, 3H, OCH3), 3.66 (dd, 1H, $J_1 = 15.65$ Hz, $J_2 = 6.38$ Hz, CH_2), 3.16 (dd, 1H, $J_1 = 15.65$ Hz, $J_2 = 4.32$ Hz, CH_2), 3.08 (m, 2H, N–CH_2–C), 2.24 (s, 3H, N–CH_3).

3.29. trans-N-Methyl-N-allyl-2-amino-6-chloro-5-hydroxy-1-phenyl-2,3-dihydro-1H-indene hydrochloride (4f)

Compound **4f** was prepared from **26** according to the procedure described for the synthesis of **4e**.

M.p. 102–104 °C; yield: 50%; IR ν_{max} (KBr): 3197 (OH), 2968 (NH^+) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 11.18–11.02 (bs, 2H, NH^+ e OH), 7.32–7.12 (m, 5H, ArH), 6.90 (m, 1H, ArH), 6.74 (m, 1H, ArH), 5.86 (m, 1H, N–C–CH=), 5.32 (m, 2H, N–C–C=CH_2), 4.82 (d, 1H, $J = 6.80$, CH–C), 4.15 (m, 1H, CH–N), 3.36 (dd, 1H, $J_1 = 15.15$ Hz, $J_2 = 6.42$ Hz, CH_2), 3.22 (dd, 1H, $J_1 = 15.15$ Hz, $J_2 = 4.33$ Hz, CH_2), 2.40 (m, 2H, N–CH_2–C), 2.02 (s, 3H, N–CH_3).

3.30. trans-N-Methyl-N-allyl-2-amino-5-chloro-6-methoxy-1-phenyl-2,3-dihydro-1H-indene hydrochloride (26)

Compound **26** was prepared from **22** according to the procedure described for the synthesis of **25**.

R_f: 0.56; yield: 60%; ^{1}H NMR ($CDCl_3$): δ 7.40–7.12 (m, 6H, ArH), 6.39 (s, 1H, ArH), 5.77 (m, 1H, N–C–CH=), 5.08 (m, 2H, N–C–C=CH_2), 4.40 (d, 1H, $J = 4.80$ Hz, CH–C), 3.70 (s, 3H, OCH3), 3.62 (m, 1H, CH–N), 3.13 (dd, 1H, $J_1 = 14.06$ Hz, $J_2 = 6.58$ Hz, CH_2), 3.07 (m, 2H, N–CH_2–C), 2.97 (dd, 1H, $J_1 = 14.06$ Hz, $J_2 = 4.58$ Hz, CH_2), 2.24 (s, 3H, N–CH_3).

3.31. trans-N-Methyl-N-allyl-2-amino-5-chloro-6-hydroxy-1-phenyl-2,3-dihydro-1H-indene hydrochloride (5f)

Compound **5f** was prepared from **23** (1.5 g, 5.2 mmol) according to the procedure described for the synthesis of **4e**.

M.p. 88–90 °C; yield: 55%; IR ν_{max} (KBr): 3185 (OH), 2947 (NH^+) cm^{-1} ^{1}H NMR (DMSO-d_6): δ 11.60–11.38 (bs, 2H, NH^+ e OH), 7.42–7.20 (m, 6H, ArH), 6.60 (m, 1H, ArH), 5.90 (m, 1H, N–C–CH=), 5.40 (m, 2H, N–C–C=CH_2), 4.92 (d, 1H, $J = 6.65$, CH–C), 4.22 (m, 1H, CH–N), 3.40 (dd, 1H, $J_1 = 14.15$ Hz, $J_2 = 6.62$ Hz CH_2), 3.28 (dd, 1H, $J_1 = 14.15$ Hz, $J_2 = 4.73$ Hz, CH_2), 2.50 (m, 2H, CH_2–C), 2.00 (s, 3H, N–CH_3).

4. Pharmacological methods

4.1. Receptor radioligand binding assays: D_1-like and D_2-like dopamine

[^{3}H]YM-09-151-2 (a D_2-like receptor antagonist, 85.5 Ci $mmol^{-1}$) and [^{3}H]SCH 23390 (a D_1-like receptor antagonist, 86 Ci $mmol^{-1}$) 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 [20]. 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^{-1} soybean trypsin inhibitor, 200 and 160 μg ml^{-1} benzamidine), using an Ultra-Turrax TP-1810 (3 × 20 s). The homogenate was centrifuged for 10 min at 50 000 × g, at 4 °C. The resulting pellet was then washed once by resuspension in fresh buffer T and centrifugation as before. The final pellet was frozen at −20 °C until the time of assay.

For D_1-like and D_2-like receptors binding assays, the porcine striatal pellet was suspended in buffer T and homogenized by Ultra-Turrax. [^{3}H]SCH 23390 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} 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}) 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 the filters was determined by a Packard 1600 TR liquid scintillation counter at 66% efficiency. Non specific 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 non-linear regression formula on a computer program (GraphPad, San Diego,

CA), were converted to K_i values according to the equation of Cheng and Prusoff [21]. Protein concentration was assayed by the method of Lowry et al. [22].

5. Results and discussion

The receptor binding properties of all final compounds were evaluated for their ability to compete with either [^{3}H]SCH 23390 or [^{3}H]YM 09-151-2 at D_1-like D_2-like binding sites, respectively, using porcine striatal membranes as tissue source. The values reported for the competitive binding assays are the average of three runs. The results of these binding studies are shown in Table 1. In order to characterize the binding assay, DA, SCH 23390 (D_1-like antagonist) and Quinpirole (D_2-like agonist) affinities were included as well.

All tested compounds were poorly effective at DA receptors (K_i nM > 1000), they were altogether devoid of selectivity. Affinity data indicate that the introduction of a chlorine atom in five or six position at 1-phenylindene nucleous decrease the affinity and D_1-like selectivity of the previously studied *trans*-2-amino-5-hydroxy-1-phenyl-2,3-dihydro-1*H*-indene ($K_i = 1.87$ nM) and *trans*-2-amino-6-hydroxy-1-phenyl-2,3-dihydro-1*H*-indene ($K_i = 2.50$ nM) [12]. Transformation of the primary amines **4a**, **5a** into *N*-alkyl and *N*,*N*-dialkyl derivatives did not affect D_1-like and D_2-like affinity and selectivity. The very slight difference in receptor affinities may indicate that there is not a favorable interaction of the varied *N*-alkyl derivatives with the binding site of receptor, with respect to the unsubstituted amines. The unfavorable interaction can be ascribed to a steric or electronic effect of the chloro substituent. However, in the isoquinoline series, Minor et al. suggested that the receptor domain could accommodate the chlorine atom and had tolerance for larger halogens such as bromine; this difference may result from a different interaction of the isoquinoline series with the DA receptors [11]. In order to evaluate the significance of the halo substituents, a search for new halo derivatives of *trans*-1-phenyl-2-aminoindane derivatives is in progress.

Acknowledgements

Financial support from Ministero dell' Università e della Ricerca Scientifica e Tecnologica (60%) and Centro di Studi per la Chimica del Farmaco-CNR (Rome) are gratefully acknowledged. The Authors thank Professor Gian Mario Cingolani for his collaboration and Domenico Rapposelli for expert technical assistance.

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