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Dopamine receptor agonists. I. Synthesis and pharmacological evaluation of 4-aryl-substituted analogues of 6,7-dihydroxy-2-amino tetralin (6,7-ADTN) and related indane compounds

G Bertolini[1], V Vecchietti*, M Mabilia**, G Norcini[1], A Restelli[2], F Santangelo[1]***, AM Villa[3], C Casagrande[1]

[1]*Medicinal Chemistry Department, Zambon Research, Via del Duca 10, 20091 Bresso, Milan;*
[2]*Istituto di Ricerche Chimiche 'G. Zambon', Zambon Group SpA, Via Cimabue 26-28, 20032 Cormano, Milan;*
[3]*Istituto di Chimica Farmaceutica, Università di Milano, Viale Abruzzi 42, 20100 Milan, Italy*

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Summary — Derivatives of *cis*- and *trans*-4-phenyl-6,7-dihydroxy-2-aminotetraline and *trans*-1-phenyl-5,6-dihydroxy-2-aminoindane were synthetized as fenoldopam analogues. They showed no affinity for D_1 and D_2 binding sites in rat striatal membranes. Molecular modeling and NMR methods used in structural comparison with fenoldopam are discussed.

dopamine / aryl rigid dopamine analogues / molecular modeling

Introduction

Structural modifications of dopamine have been investigated with the aim of providing orally active analogues endowed with selectivity for either, or both, the dopamine receptor subtypes D_1 and D_2. Rigid 2-aminotetraline and 2-aminoindane derivatives exhibited marked activity [1–3]. In particular, 6,7-dihydroxy-2-aminotetrahydronaphthalene (6,7-ADTN) was shown to primarily stimulate D_1 receptors, while its N,N-di-n-propyl derivative was remarkably more active on D_2 receptors; these compounds however retained β- and α-adrenergic activity, and were not active by oral administration.

Enclosing the dopamine structure in the semirigid structure of 7,8-dihydroxy-tetrahydro-3H-3-benzazepine preserved some degree of dopaminergic activity; the insertion of a phenyl group in the 4-position resulted in compound SK&F 38393 having marked activity and selectivity for the D_1 receptor, as well as an acceptable oral bioavailability [4]. Further structural modifications led to fenoldopam (fig 3) which showed similar properties and a peripheral distribution, and was proposed as a vasodilator acting on peripheral D_1 receptors [5].

We have synthetized the 4-aryl analogues of 6,7-ADTN and the 1-aryl analogues of 5,6-dihydroxy-2-aminoindane in order to investigate the effects of this structural modification in these series (fig 1).

Chemistry

The synthetic route we followed to synthesize these compounds is reported in schemes 1–5.

Crotonic condensation of 3,4-dimethoxyphenyl-2-propanone, 4, [6] with benzaldehyde, followed by an acid cyclization, gave ketone **6** which was immediately reduced with sodium borohydride in methanol, yielding the *cis*-alcohols 7 and *trans*-alcohol 10 in 85:15 ratio. The pure alcohol 7 was obtained by crystallization. These results are in agreement with the preferential axial attack of a nucleophile on a cyclohexanone [7]. The prevailing formation of the *cis*-alcohol 7 can be explained considering the most stable conformation of 6 having the phenyl group in the pseudoequatorial position. In order to synthesize the diastereoisomeric alcohol 10, 7 was converted into its methane-sulphonate 8 (scheme 1), and the configuration at C_2 was inverted by SN_2 substitution

*Present address: Zambeletti SpA, Baranzate di Bollate, Milan, Italy.
**Computer-Aided Drug Design Consultant.
***Correspondence and reprints.

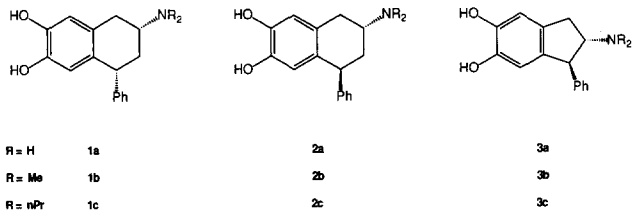


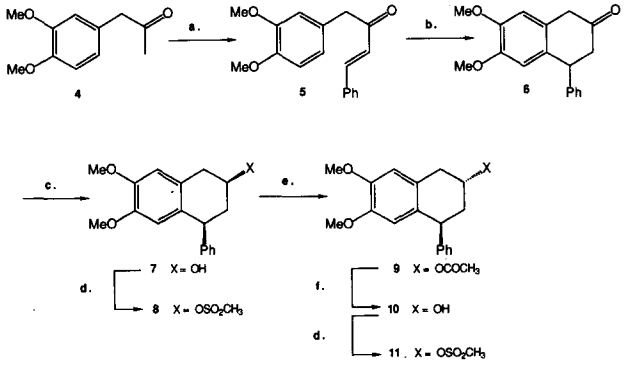
Fig 1. Structures of 4-aryl analogues of 6,7 ADTN and 1-aryl analogues of 5,6-dihydroxy-2-aminoindane.

with an acetoxy group as nucleophile. Alcohol 10 was similarly converted into its methanesulphonate 11. Reaction of 8 and 11 with sodium azide followed by catalytic hydrogenation gave amines 12 and 15 respectively (scheme 2); acid hydrolysis of the dimethoxy group gave the primary amines 1-a and 2-a. Dialkylation of 12 and 15 followed by acid hydrolysis afforded the N,N-disubstituted compounds **1b–c** and **2b–c**.

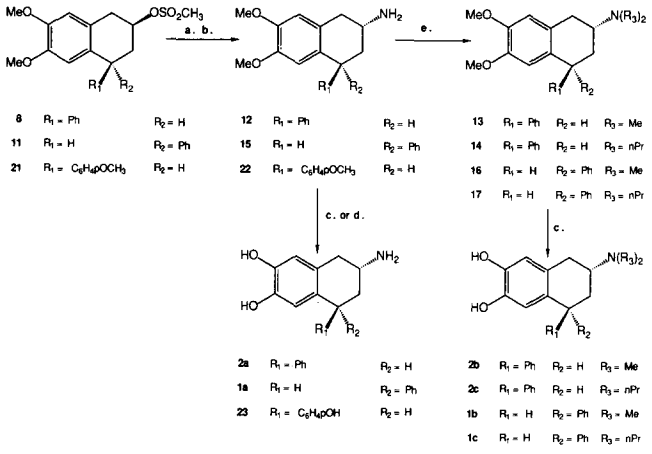
The relative configuration of the two series of compounds **1** and **2** was elucidated using ^{1}H-NMR (200 MHz) experiments on methanesulphonate 8 and 11 and was confirmed with ^{1}H-NMR (300 MHz) experiments on the final products 1a and 2a.

A similar approach (scheme 3) was applied in the synthesis of the 4'-hydroxyderivative 23. In this case, starting from 4 [6] the tetralone 19 was obtained *via* aldol condensation, with *p*-methoxybenzaldehyde followed by acid cyclization. Thereafter, the *trans*-amine 23 was obtained from the *cis*-alcohol 20 by the same sequence of scheme 1 and 2.

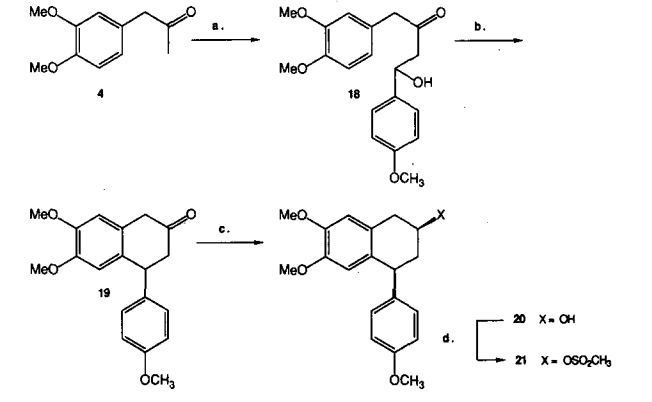
On the other hand, this synthetic approach does not appear to be suitable for compounds **3a–c** because corresponding methanesulphonates would easily



Scheme 1. a) PhCHO, NaOH, H_2O, 60°C/24 h. b) PPA, 50°C/2 h. c) $NaBH_4$, MeOH. d) CH_3SO_2Cl, Py. e) $CH_3COONEt_4 \cdot 4\ H_2O$, acetone. f) LAH, THF, 25°C.

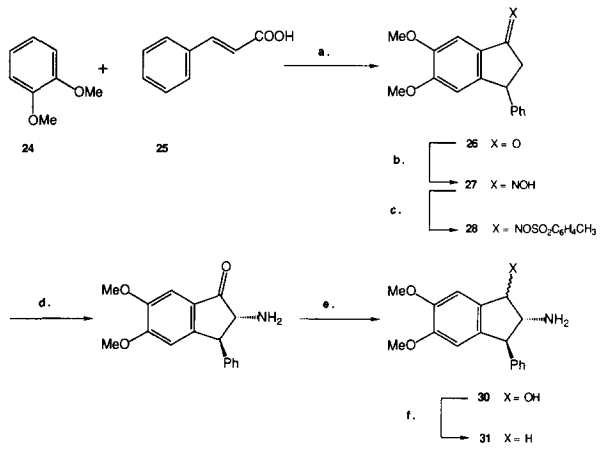


Scheme 2. a) NaN_3, DMF, 60°C/3 h. b) H_2, Pd/C 10%, EtOH. c) HBr 40%, 130°C/3 h. d) BBr_3, CH_2Cl_2. e) R = Me: HCOOH, HCOONa, HCHO, DMF, 100°C/3 h; R = Pr: n-Pr-Br, K_2CO_3, DMF, 65°C/6 h.



Scheme 3. a) LDA, p-$OCH_3C_6H_4CHO$, –78°C. b) PPA, 50°C, 2 h. c) $NaBH_4$, MeOH. d) CH_3SO_2Cl, Py.

undergo elimination instead of substitution. The synthesis was achieved by the sequence outlined in scheme 4. An acid cyclization of veratrole 24 and cinnamic acid 25 yielded the ketone 26, which was converted into its *O*-tosyloxime. Neber rearrangement gave the amino ketone 29 (scheme 4). We obtained the pure *trans* stereoisomer as expected from the equilibration at the carbon 2 to the most thermodynamically stable compound under the strongly basic conditions which were employed. Reduction to alcohol was followed by hydrogenolysis yielding the amine 31. The final compounds **3a–c** were obtained (scheme 5) with the same scheme which was used for the tetraline compounds. The relative stereochemistry



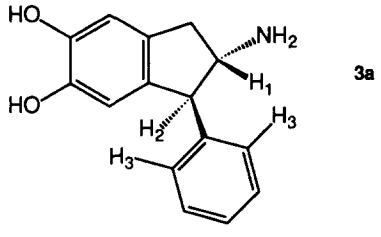
Scheme 4. a) PPA, 95°C/4 h. b) NH_2OH•HCl, MeOH, K_2CO_3, H_2O, reflux/2 h. c) PTSCl, Py. d) EtONa, EtOH, Toluene. e) $NaBH_4$, MeOH. f) H_2, Pd/C 10%, EtOH.

of compounds **3a–c** was elucidated using a NOE experiment on compound **3a** in which NOE (4.5%) was observed between H_1 and H_3 in agreement with the *trans* configuration of the product (fig. 2).

Pharmacology

The affinities of compounds **1a–c**, **2a–c**, **3a–c** and **23** for dopaminergic receptors were tested in a binding assay using the D_1 selective ligand [^{3}H]-SCH 23390 (0.2 nM) and the D_2 selective ligand [^{3}H]-domperidone (0.3 nM) on rat striatum membranes prepared according to Billard [8]. The values of K_D and B_{max} were 0.63 µM and 1643 fmol/mg of proteins for SCH 23390, 0.60 µM and 8.39 fmol/mg for domperidone.

Compounds **1a–c**, **2a–c**, **3a–c** and **23** did not show any significant affinity to the central dopaminergic receptors.



3a

Fig 2. Relative configuration of compound **3a** assigned by NOE.

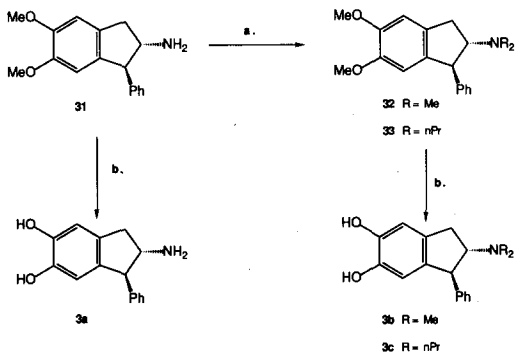
Molecular modeling and NMR studies

Whereas potency (or lack of) may depend on a variety of factors (absorption, pharmacokinetic and metabolism profile), affinity mainly depends on the capability of a given compound to fit and favorably interact at a binding site. Therefore, conformational analyses and subsequent structure superpositions were employed in an attempt to rationalize the lack of affinity.

The compounds considered in this molecular modeling study are shown in figure 3. Three-dimensional models of fenoldopam, 6,7-ADTN and 1-phenyl-2-amino-5,6-dihydroxyindane were generated using a 2D-to-3D builder available in Chem-X [9] and starting from SMILES notations [10].

Each one of the possible aminotetralin (with the 2R configuration) and aminoindane stereoisomers were generated and their geometries were subsequently optimized, using two different methods for comparison purposes: 1) the MM free-valence-geometry force field and the conjugate-gradient minimizer OPTIMISE in Chem-X, and 2) Allinger's MM2 [11]. A Coulombic electrostatic term was employed in Chem-X MM energy minimizations, with a dielectric constant of 1 and partial atomic charges obtained by the Gasteiger-Marsili method [12]. Dipole interaction energies, based on bond moments, were computed in MM2. All molecules were studied in a neutral state, *ie* the amino moieties were not protonated. All calculations were performed *in vacuo*. Molecular mechanics energy values are given in kcal/mol.

Only one conformation of fenoldopam was considered in this study, with the seven-membered ring in a chair conformation and the phenyl group in equatorial position. Such a conformation, which corresponds to the global minimum energy conformation, was chosen on the basis of: 1) force field calculations and D-1 receptor affinity data of benzazepine analogs [13] which led to the conclusion that an axial phenyl ring is detrimental to D-1 receptor affinity. In fact, compounds where the phenyl ring is fixed in an equatorial orientation through ring closure possess higher affinity and selectivity towards the D-1 receptor. 2) MM2 conformational analysis and experimental receptor binding data reported in the literature [14] on a set of dopamine D-1 agonists of the benzazepine series. Following an elegant and logic line of reasoning which takes advantage of conformationally constrained analogs, the conclusion of the above mentioned paper is that the biologically active conformation is a chair conformation with an equatorial phenyl ring. Conformational analyses were carried out using Chem-X to generate starting aminotetralin and aminoindane conformations to be followed by energy minimizations.



Scheme 5. a) R = Me: HCOOH, HCOONa, HCHO, DMF, 100°C/3 h; R = n-Pr: n-Pr-Br, K_2CO_3, DMF, 65°C/6 h. b) HBr 40%, 130°C/3 h.

The distance geometry program DGEOM [15] and a β-test version of the Chem-X DGEOM interface, were employed to perform pharmacophore matching. A tentative pharmacophore was defined for fenoldopam and all of the other structures included in the study. This pharmacophore (fig 3) is characterized by the two catechol oxygen atoms (denoted as O1 and O2 in fig 3), the amino nitrogen (N in fig 3), the geometric centers of the two aromatic rings (points A and B, respectively, in fig 3). The DGEOM program generates one or more conformations for each one of the stereoisomers. At the same time, it tries to match the pharmacophoric points O1, O2, N, A, B in the current compound onto the corresponding points in fenoldopam. The fenoldopam model was held fixed in the chosen 'active' conformation and used as a template. Each one of the geometries obtained from DGEOM was then allowed to relax by energy minimization (MM2) to ensure that the resulting conformation is energetically accessible. A rigid fit was then performed onto fenoldopam.

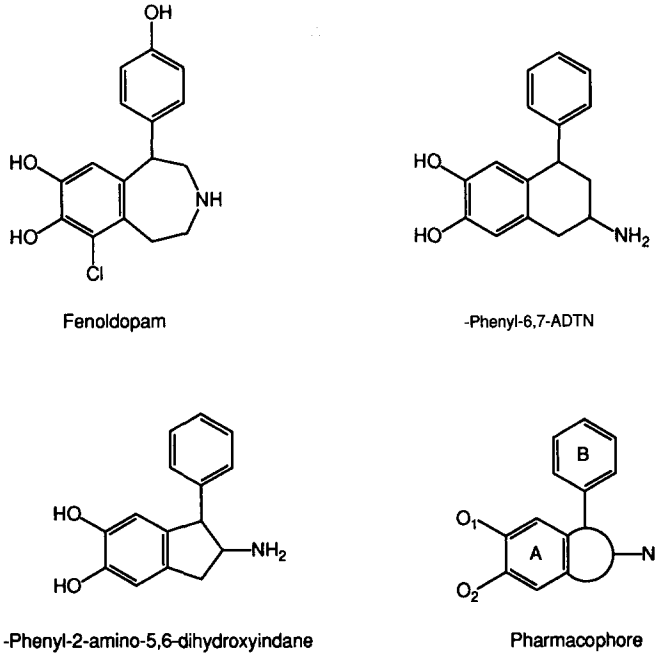


Fig 3. Structures included in the study and schematic representation of the pharmacophore.

The results of molecular mechanics energy minimizations, obtained by Chem-X MM and MM2, for the stereoisomers of 4-aryl 6,7-ADTN are reported in table Ia. The root mean square (rms) distances between all pairs of equivalent atoms in corresponding conformers obtained by the two methods are between 0.04 and 0.07 Å.

In agreement with NMR results, the lowest energy conformation for **1a** is a half-chair with the amino and phenyl groups in pseudo-equatorial positions. The global minimum energy conformation for 2-(*R*),4-(*S*) isomer is a half-chair with the amino function in the equatorial position and the phenyl ring in pseudo-axial position.

The energy values reported in table Ib correspond to the conformations generated by DGEOM, using fenoldopam as a rigid template. Such conformations do not correspond to optimized geometries (*ie* they are not conformers). They simply represent the best possible fit to fenoldopam. In order to match the pharmacophore points O1, O2, N, A and B of aminotetralins with the corresponding points of fenoldopan, DGEOM generated a boat conformation (with axial amino group and equatorial phenyl ring) for the 2-(*R*),4(*R*) isomer and a distorted half-chair (with axial amino group and pseudo-equatorial phenyl ring) for the 2-(*R*),4-(*S*) isomer. The fit of 2-(*R*),4-(*S*) onto fenoldopam is illustrated in figure 4. Although this, as well as other fittings generated by the DGEOM, may look quite good, the corresponding aminotetralin conformations are not likely to be adopted: in fact, according to Boltzmann's distribution law, they are scarcely populated because of their high energies.

The conformers obtained by energy minimization starting from the DGEOM results are described in table Ic. In the process of minimizing the energy, the quality of the fit onto fenoldopam deteriorated, as can be seen in figure 5 for the 2-(*R*),4-(*S*) isomer. In particular, while the fit is still acceptable in terms of O1, O2, N, A, it is the 4-phenyl group which does not fit onto the corresponding moiety in fenoldopam. This observation may account for the lack of dopaminergic activity of this class of compounds.

Table I. Results of molecular mechanics and DGEOM calculations.

Isomer	*Conformation*	*Amino*	*Phenyl*	*MM2P En*	*MM2P Delta En*	*CHEM-X MM Ener*	*CHEM-X Delta En*
Lowest En conform[a]							
2-R,4-R	Half-chair	Equatorial	Pseudo-eq	2.16	0.00	17.64	0.00
2-R,4-S	Half-chair	Equatorial	Pseudo-axial	2.84	0.68	17.76	0.12
After DGEOM[b]							
2-R,4-R	Boat	Axial	Equatorial	16.11	13.95	–	–
2-R,4-S	Half-chair	Axial	Pseudo-eq	9.57	7.41	–	–
After minimization[c]							
2-R,4-R	Half-chair	Axial	Pseudo-axial	4.39	2.23	19.19	1.55
2-R,4-S	Half-chair	Axial	Pseudo-eq	2.99	0.83	17.98	0.34

[a]Minimum–energy conformations; [b]energy values of the same structures as obtained by DGEOM; [c]minimum energy conformations obtained using DGEOM results as starting points

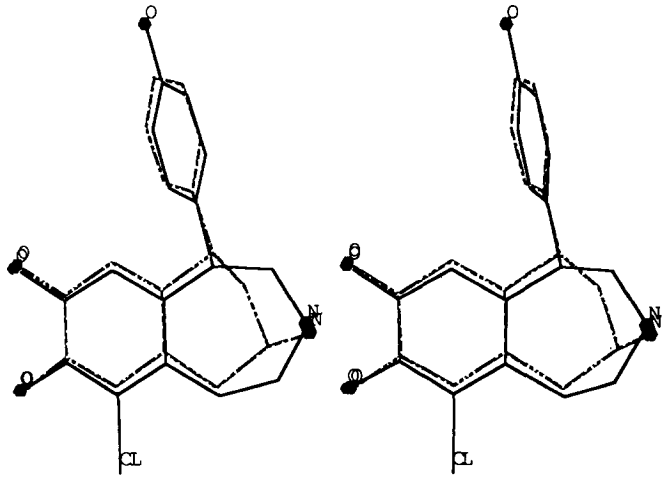


Fig 4. 2-R,4-S from DGEOM (dashed line) onto Fenoldopam.

Molecular mechanics energy minimizations were also carried out for the stereoisomers of 1-phenyl-2-amino-5,6-dihydroxyindanes, employing the two puckered ('up' and 'down') conformations of cyclopentene as starting geometries. No results could be obtained by DGEOM for these amino-indanes, employing the pharmacophore already definied and fenoldopam as a template. As previously described for the aminotetralin compounds, the phenyl group is again responsible for the poor quality of the fit onto fenoldopam.

We have examined *via* ^{1}H-NMR compounds **1a** and **2a** (fig 1). For each of them, the proton chemical shift assignments in DMSO-d_6 solution, presented in tables II and III, are determined *via* mono- and bidimensional NMR techniques. The value of the coupling constants are extracted from the spectra after selective homonuclear spin decoupling when necessary.

^{1}H NOE experiments on **1a**, carried out with variable mixing time, show interactions between (H_4)-(H_2) and (H_4)-($H_{3\beta}$). These interactions are evidence of a half-chair conformation of the saturated ring, with the NH_2, the phenyl and $H_{3\beta}$ in pseudo-equatorial position, the H_4, $H_{3\alpha}$ and H_2 in pseudo axial arrangement. Assignment of this conformation is supported

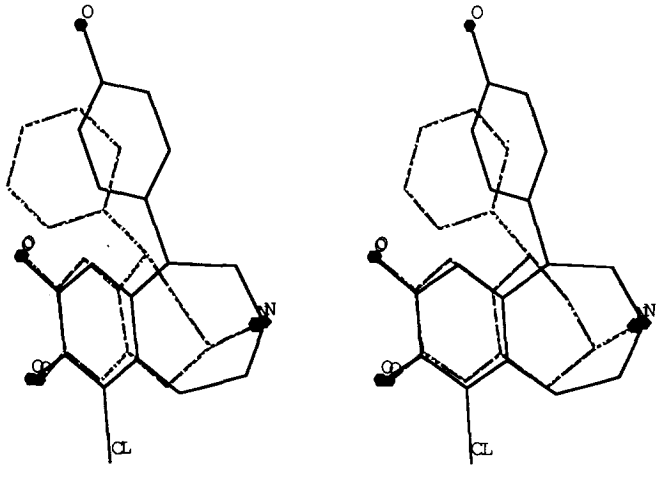


Fig 5. 2-R,4-S after minimization (dashed line) onto Fenoldopam.

Table II. Chemical shifts and ^1H coupling constant of compound **Ia** in DMSO-d_6. The chemical shifts are expressed in ppm (δ) and are related to the tetramethylsilane; s = singlet, d = doublet.

^1H type	δ	Pattern	Coupling constants (Hz)
$H_{1\alpha}$	2.42	dd	$J_{1\alpha,1\beta} = 15.4$; $J_{1\alpha,2} = 11.0$
$H_{1\beta}$	2.72	dd	$J_{1\beta,1\alpha} = 15.4$; $J_{1\beta,2} = 5.7$;
H_2	3.00	dddd	$J_{2,1\alpha} = 11.0$; $J_{2,1\beta} = 5.7$; $J_{2,3\alpha} = 12.2$; $J_{2,3\beta} = 3.0$
$H_{3\alpha}$	1.50	ddd	$J_{3\alpha,3\beta} = 12.2$; $J_{3\alpha,2} = 12.2$; $J_{3\alpha,4} = 12.2$
$H_{3\beta}$	2.00	ddd	$J_{3\beta,3\alpha} = 12.2$; $J_{3\beta,2} = 2$; $J_{3\beta,4} = 5.5$
H_4	3.90	dd	$J_{4,3\alpha} = 12.2$; $J_{4,3\beta} = 5.5$
H_4	6.00	s	–
H_8	6.45	s	–

Table III. Chemical shifts and ^1H coupling constant of compound **2a** in DMSO-d_6. The chemical shifts are expressed in ppm (δ) and are related to the tetramethylsilane; s = singlet, d = doublet.

^1H type	*δ*	*Pattern*	*Coupling constants (Hz)*
$H_{1\alpha}$	2.30	dd	$J_{1\alpha,1\beta} = 15.8$; $J_{1\alpha,2} = 8.7$
$Hl_{1\beta}$	2.80	dd	$J_{1\beta,1\alpha} = 15.8$; $J_{1\beta,2} = 4.9$;
H_2	2.95	dddd[a]	$J_{2,1\alpha} = 8.7$; $J_{2,1\beta} = 4.9$
$H_{3\alpha}$	1.80	m[a]	$J_{3\alpha,4} = 5.25$
$H_{3\beta}$	1.80	m[a]	$J_{3\beta,4} = 5.25$
H_4	4.10	dd	$J_{4,3\alpha} = 5.25$; $J_{4,3\beta} = 5.25$
H_5	6.18	s	–
H_8	6.48	s	–

[a]Since $H_{3\alpha}$ and $H_{3\beta}$ overlap the determination of $J_{3\alpha,3\beta}$; $J_{2,3\alpha}$; $J_{2,3\beta}$ are not possible

by the coupling constant data. $H_{3\alpha}$ has the same coupling constant, 12.2 Hz, with H_2 and H_4. This is possible if the $H_{3\alpha}$ is in anti position with respect to the both hydrogens H_2 and H_4.

The NOESY experiments of **2a** reveal NOE between H_2 and *ortho*-hydrogens of the phenyl group in position 4, between H_4 and both $H_{3\alpha}$ and $H_{3\beta}$, and between H_5 and with $H_{3\alpha}$ and/or $H_{3\beta}$ are obtained. The above NOE's suggest once again a half-chair conformation of saturated ring. Here the NH_2 and H_4 are pseudo equatorial; the phenyl group, the $H_{3\alpha}$ and H_2 are pseudo axial.

The coupling constants of H_2 with $H_{1\alpha}$ (8.7 Hz) and $H_{2\beta}$ (4 9 Hz) support a half-chair conformation, with H_2 in the pseudo axial arrangement; however the coupling constant data of H_4 with $H_{3\alpha}$ and $H_{3\beta}$ (5.25 Hz) do not support the half-chair conformation. In a half-chair, H_4 should have a different coupling constant for each of the two H_3 hydrogens. It is likely that the structure in solution is the average contribution of two differently populated half-chair conformations, one with the phenyl pseudo axial, and the other with the phenyl pseudo equatorial. This result is in agreement with the difference in energy of these two conformations as the compound **2a** is only 0.15 kcal/mol (tables Ia and Ic).

Conclusion

The investigation of the conformational features of the investigated compounds by combining molecular modeling and NMR methods, and the comparison with fenoldopam provided a clue to understanding the lack of pharmacological activity. Further work on related compounds is in progress, in order to confirm the validity of the methodological approach.

Experimental protocols

Melting points were taken in open capillary tubes and were uncorrected. Proton nuclear magnetic resonance (^1H-NMR) spectra were obtained on a Varian XL-300 instrument, operating at 300 MHz or on a Varian XL-200 instrument, operating at 200 MHz. Samples (10–20 mg) were dissolved in $CDCl_3$ or DMSO-d_6. Chemical shifts (δ) are reported in ppm downfield from internal tetramethylsilane. ^1H-NMR data are reported in the following order: chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet; br, broad) and number of protons. Mass spectra were obtained on a Varian CH in electron impact. Elemental analyses were performed on a Perkin Elmer 240 B instrument and are indicated by elemental symbols only when the results were within ± 0.4% of the theoretical values. All chemicals and solvents were analytical grade and were used without further purification. The reactions were carried out under nitrogen when required. Organic layer was dried on Na_2SO_4.

Molecular modeling and NMR measurements

Molecular modeling calculations were run on a Digital microVAX 2000 with 6 Mb of RAM and graphic manipulations were performed either on an Apricot Sigmex 6268 or on a Mac IIci (with a RasterOps graphics device) connected to the VAX.

All spectra were recorded with a Varian XL 300 spectrometer operating at 299.997 MHz. The 2D-NOESY experiments were carried out with several mixing times from 0.1–1 in phase sensitive mode; the 90 pulse was 12 μs and a relaxation delay of 6 s, 5 time greater than the longest T_1 to ensure peak determination. The data matrixes were 1024 x 1 024 256 increments and 256 transient for each FID. The temperature was controlled at 300 K for all experiments. ^1H spin-lattice relaxation times were measured by the inversion recovery method. The solution of **1a** or **2a** was prepared by dissolving approximately 7 mg of compound in 1 ml of deuterio-dimethylsulphoxide. The solution was transferred to a previously constricted 5 mm tube and degassed by several freeze-pump-thaw cycles on a high-vacuum line to remove dissolved oxygen.

1-(3,4-dimethoxyphenyl)-4-phenyl-3-buten-2-one, 5
Benzaldehyde (51 g, 481 mmol) and 3,4-dimethoxyphenyl-2-propanone, 4 (90 g, 0.464 mmol) were added to a solution of sodium hydroxide (3.75 g, 94 mmol) in water (1600 ml) pre-heated at 55°C. The mixture was stirred for 24 h, then cooled. The solid was filtered, washed with hot ethanol (300 ml) and dried, affording 84.2 g (64%) of 5 as pale yellow crystals, mp 145–147°C. ^{1}H-NMR ($CDCl_3$ 300 MHz): δ ppm 3.87 (s, 6H); 6.76 (s, 1H); 6.78 (d, 1H); 6.81 (d, 1H); 6.83 (s, 1H); 6.84 (d, 1H); 7.37 (m, 3H); 7.51 (dd, 2H); 7.63 (d, 1H).

6,7-dimethoxy-4-phenyl-2-tetralone, 6
In a nitrogen atmosphere, **5** (30 g, 106 mmol) was added to polyphosphoric acid (250 g) vigorously stirred at 50°C. After 2 h at 50°C, water (100 ml) was added. After complete dissolution, the solution was extracted with ether (4 x 250 ml). The extracts were washed with water, dried (Na_2SO_4), and evaporated under reduced pressure to give 23.5 g of crude **6**, which was immediately reduced. ^{1}H-NMR ($CDCl_3$ 300 MHz): δ ppm 2.91 (d, 2H); 3.52 (d, IH); 3.60 (d, IH); 3.74 (s, 3H); 3.88 (s, 3H); 4.41 (t, lH); 6.53 (s, lH); 6.67 (s, lH); 7.09 (d, 2H); 7.20–7.35 (m, 3H).

cis-6,7-dimethoxy-4-phenyl-2-hydroxytetralin, 7
Sodium borohydride (4.13 g, 110 mmol) was added to **6** (25 g, 89 mmol) dissolved in methanol (250 ml), and the mixture was stirred for 3 h at room temperature. Water (500 ml) was then added and the mixture was evaporated under reduced pressure and extracted with methylene chloride (2 x 250 ml). The combined extracts were dried (Na_2SO_4) and evaporated. The resulting oil was crystallized from ethyl ether; yielding 10 g (35%) of **7** as a white solid; mp 123–125°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ ppm 1.62 (bd, OH); 1.86 (dt, lH); 2.37 (dddd, 1H); 2.85 (dd, lH); 3.10 (ddd, lH); 3.58 (s, 3H); 3.87 (s, 3H); 4.10 (dd, lH); 4.17 (dddd, lH); 6.23 (s, lH); 6.59 (s, lH), 7.75 (m, SH).

cis-6,7-dimethoxy-4-phenyl-2-methanesulphonyloxytetralin, 8
Methanesulphonylchloride (9.2 g, 80 mmol) was added to a stirred solution of **7** (22.8 g, 80 mmol) in pyridine (40 ml). After 45 min at room temperature, the mixture was poured into water (100 ml). The precipitate was collected by filtration and washed with water. Crystallization from ethanol gave 24.8 g (88%) of **8** as white crystals; mp 131–133°C. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ ppm 2.11 (dt, 1H); 2.57 (dddd, 1H); 3.00 (s, 3H); 3.15 (bdd, lH); 3.28 (ddd, 1H); 3.60 (s, 3H); 3.98 (s, 3H); 4.17 (dd, lH); 5.12 (dddd, lH); 6.25 (s, lH); 6.62 (s, IH); 7.25 (m, SH).

Trans-6,7-dimethoxy-4-phenyl-2-acetoxytetralin, 9
Tetraethylammonium acetate tetrahydrate (63 g, 300 mmol) was added to a solution of **8** (36.5 g, 100 mmol) in acetone (150 ml) and the solution was refluxed for 7 h. After cooling, the solvent was evaporated leaving an oil, which was chromatographed on silica gel column, with a mixture of cyclohexane-ethyl acetate, 9:1, as the eluent to yield 22.8 g (70%) of **9**, mp 69–70°C (from hexane). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ ppm 2.04 (s, 3H); 2.05 (ddd, lH); 2.30 (ddd, lH); 2.85 (dd, lH); 3.23 (dd, lH); 3.64 (s, 3H); 3.87 (s, 3H); 4.23 (dd, lH); 5.23 (m, lH); 5.68 (s, 1H); 6.60 (s, lH); 7.10 (d, 2H); 7.26 (m, 3H); MS m/e 326.

Trans-6,7-dimethoxy-4-phenyl-2-hydroxytetralin, 10
A solution of **9** (22.8 g, 70 mmol) in THF (100 ml) was added dropwise to a suspension of lithium aluminium hydride (1.5 g, 30 mmol) in THF (30 ml) with stirring under nitrogen atmosphere. The mixture was stirred at room temperature for a further 18 h, the excess of hydride was decomposed by careful addition of water, the salts were filtered off; the filtrate was extracted with CH_2Cl_2. The organic phase was dried (Na_2SO_4) and evaporated to give an oil. Crystallization, from ethyl ether gave 18.9 g (95%) of **10** as a white solid, mp 117–119°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ ppm 1.60 (bs, exchange with D_2O); 2.05 (ddd, lH); 2.20 (ddd, lH); 2.76 (dd, lH); 3.15 (dd, lH); 3.66 (s, 3H); 3.88 (s, 3H); 4.20 (m, lH); 4.30 (dd, lH); 6.38 (s, lH); 6.63 (s, lH); 7.07 (d, 2H); 7.25 (m, 3H).

Trans-6,7-dimethoxy-4-phenyl-2-methanesulphonyloxy-tetralin, 11
Compound **11** was obtained starting from **10** in the same way as **8**, in 89% yield as white crystals (20.3 g, 89%), mp 120–122°C (from ethanol). ^{1}H-NMR ($CDCl_3$, 200 MHz): ppm 2.15 (ddd, lH); 2.48 (ddd, 1H); 2.90 (s, 3H); 3.10 (dd, lH); 3.32 (dd, lH); 3.62 (s, 3H); 3.88 (s, 3H); 4.32 (dd, lH); 5.18 (dddd, lH); 6.35 (s, lH); 6.62 (s, lH); 7.1–7.3 (m, 5H).

Trans-6,7-dimethoxy-4-phenyl-2-aminotetralin hydrochloride, 12
Sodium azide (6.3 g, 97 mmol) was added to a solution of **8** (23.6 g, 65 mmol) in *N,N*-dimethylformamide (150 ml). The mixture was heated at 60°C and stirred for 3 h. After cooling, water (500 ml) was added and the mixture was extracted with ethyl acetate (2 x 200 ml). Washing of the extract with brine, drying and evaporating resulting in an oil that was dissolved in ethanol (100 ml) and hydrogenated in Parr apparatus over 10% palladium-on-charcoal at 40 psi at room temperature. After absorption of the theoretical volume of hydrogen, the catalyst was filtered off and the solvent evaporated. The resulting oily base was dissolved in ethanol and acidified with anhydrous hydrogen chloride. The crystalline salt was filtered to give 20 g (96%) of **12** as a white solid, mp 175–177°C. ^{1}H-NMR (DMSO-d_6, 300 MHz): δ ppm 2.15 (m, 2H); 2.80 (dd, lH); 3.20 (m, 2H); 3.56 (s, 3H); 3.75 (s, 3H); 4.35 (dd, lH); 6.41 (s, lH); 6.80 (s, lH); 6.98 (d, 2H); 7.19 (t, lH); 7.29 (dd, 2H); 8.30 (bs, exchange with D_2O).

Trans-6,7-dihydroxy-2-phenyl-2-aminotetralin hydrobromide, 2a
A solution of **12** (3.3 g, 10 mmol) in 40% hydrobromic acid (40 ml) was refluxed for 3 h. After cooling, the mixture was diluted with ethanol (100 ml) and evaporated under reduced pressure. The residue was dissolved in ethanol (100 ml) and the solvent was removed again. The product was crystallized from a mixture ethanol/ethyl acetate 1/1, yielding 2.7 g (80%) of **2a** as the hydrobromide, mp 242–244°C. Anal $C_{16}H_{17}NO$. HBr (C, H, Br, N). ^{1}H-NMR (DMSO-d_6), 300 MHz: δ ppm 2.10 (m, 2H); 2.68 (dd, 1H); 3.30 (m, lH); 4.20 (dd, lH); 6.21 (s, lH); 6.55 (s, 1H); 7.00 (d, 2H); 7.18 (t, 1H); 7.30 (dd, 2H); 7.90 (bs, exchange with D_2O); 8.72 (s, exchange with D_2O); 8.80 (s, exchange with D_2O).

Trans-6,7-dimethoxy-4-phenyl-2(N,N-dimethyl)aminotetralin hydrochloride, 13
Formic acid 88% (4 ml, 89 mmol) and formaldehyde 32% (8.4 ml, 81 mmol) were slowly added to a stirred solution of **12** (6.1 g, 19 mmol) and sodium formate (1.36 g, 20 mmol) in DMF (50 ml). The solution was stirred at 100°C for 3 h. After cooling, water (100 ml) was added. The mixture was made alkaline with sodium hydroxide and was extracted with dichloromethane (2 x 100 ml). The combined extracts were dried (Na_2SO_4) and evaporated. The residue was converted to the hydrochloride salt and crystallized from ethyl acetate to give **13** (3.8 g, 57%), mp 182–184°C. ^{1}HNMR (DMSO-d_6, 300 MHz): δ ppm 2.30 (m, 2H); 2.65 (s, 6H); 3.00 (dd, 1H);

3.22 (dd, 1H); 3.58 (s, 3H); 3.77 (s, 3H); 4.41 (dd, 1H); 6.48 (s, 1H); 6.80 (s, 1H); 6.98 (d, 2H); 7.20 (t, 1H); 7.28 (dd, 2H).

*Trans-6,7-dihydroxy-4-phenyl-2-(N,N-dimethyl)aminotetralin hydrobromide, **2b***
Compound **2b** was synthesized from **13** in the same manner as **2a** in 66% yield, mp 234–236°C. Anal $C_{18}H_{21}NO_2$·HBr (C, H, Br, N). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ ppm 2.22 (m, 2H); 2.70 (m, 6H); 2.88 (dd, 1H); 3.05 (dd, 1H); 3.35 (m, 1H); 4.28 (dd, 1H); 6.26 (s, 1H); 6.60 (s, 1H); 7.02 (d, 2H); 7.20 (t, 1H); 7.28 (dd, 2H); 8.80 (s, exchange with D_2O); 9.6 (bs, exchange with D_2O).

*Trans-6,7-dihydroxy-4-phenyl-2-(N,N-di-n-propyl)amino-tetralin hydrobromide, **2c***
1-Bromopropane (3.64 ml, 40 mmol) was added to a mixture of 12 (6.4 g, 20 mmol) and potassium carbonate (5.52 g, 40 mmol) in DMF (25 ml) and the mixture was stirred at 65°C for 6 h. After cooling water (50 ml) was added and the product was extracted with CH_2Cl_2 (2 x 50 ml). Evaporation of the solvent gave crude **15**, that was boiled in hydrobromic acid 40% (40 ml) for 3 h. After cooling, ethanol (100 ml) was added and the solution was evaporated under reduced pressure. The residue was crystallized from ethyl acetate to give 3.36 g (40%) of **2c**, mp 187–189°C. Anal $C_{22}H_{19}NO_2$·HBr (C, H, Br, N). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ ppm 0.80 (t, 3H); 0.85 (t, 3H); 1.33–1.53 (m, 4H); 2.16 (bd, 1H); 2.31 (ddd, 1H); 3.02 (m, 6H); 3.40 (m, 1H); 1.33 (m, 1H); 6.29 (s, 1H); 6.61 (s, 1H); 7.02 (d, 2H); 7.21 (t, 1H); 7.30 (dd, 2H); 8.78 (s, exchange with D_2O); 8.88 (s, exchange with D_2O); 9.10 (bs, exchange with D_2O).

*Cis-6,7-dimethoxy-4-phenyl-2-aminotetralin hydrochloride, **15***
Compound **15** was synthetized from **11** in the same manner as **12** in 89% yield, as a white solid. mp 254–256°C. ^{1}H-NMR (DMSO-d_6, 300 MHz): δ ppm 1.83 (ddd, 1H); 2.32 (m, 1H); 2.95 (dd, 1H); 3.10 (dd, 1H); 3.41 (s, 3H); 3.50 (m, 1H); 3.74 (s, 3H); 4.15 (dd, 1H); 6.10 (s, 1H); 6.78 (s, 1H); 7.17 (d, 2H); 7.26 (t, 1H); 7.35 (t, 2H); 8.40 (bs, exchange with D_2O).

*Cis-6,7-dihydroxy-4-phenyl-2-aminotetralin hydrobromide, **la***
Cornpound **la** was synthetized from **15** in the same manner as **2a** in 95% yield, mp 263–265°C. Anal $C_{16}H_{17}NO_2$. HBr (C, H, Br, N). ^{1}H-NMR (DMSO-d_6, 300 MHz): ppm 1.78 (dd. 1H); 2.22 (bd, 1H); 2.81 (dd, 1H); 2.95 (dd, 1H); 3.35 (s, exchange with D_2O); 3.50 (m, 1H); 4.02 (dd, 1H); 6.02 (s, 1H); 6.50 (s, 1H); 7.16 (d, 2H); 7.24 (t, 1H): 7.35 (dd, 2H); 8.12 (bs, exchange with D_2O); 8.68 (bd, exchange with D_2O).

*Cis-6,7-dimethoxy-4-phenyl-2-N,N-dimethylaminotetralin hydrochloride, **16***
Compound **16** was synthetized from **15** in the same manner as **13** in 88% yield, mp 216–218°C. ^{1}H-NMR (DMSO-d_6, 300 MHz): δ ppm 1.92 (dd, 1H); 2.47 (bdd, 1H); 2.78 (t, 6H); 3.15 (m, 2H); 3.41 (s, 3H); 3.66 (m, 1H); 3.74 (s, 3H); 4.12 (dd, 1H); 6.10 (s, 1H); 6.75 (s, 1H); 7.20 (d, 2H); 7.28 (t, 1H); 7.36 (dd, 2H).

*Cis-6,7-dihydroxy-4-phenyl-2-N,N-dimethylaminotetralin hydrobromide, **lb***
Compound **1b** was synthetized from **15** in the same manner as **2a** in 89% yield, mp 258–260°C. Anal $C_{18}H_{21}NO_2$·HBr (C, H, N, Br). ^{1}H NMR (DMSO-d_6, 300 MHz): δ ppm 1.88 (dd, 1H); 2.36 (bdd, 1H); 2.80 (t, 6H); 3.00 (m, 2H); 3.50 (bs, exchange with D_2O); 3.69 (bdd, 1H); 4.02 (dd, 1H); 6.01 (s, 1H); 6.52 (s, 1H); 7.20 (d, 2H); 7.26 (t, 1H); 7.36 (dd, 2H); 8.70 (bs, exchange with D_2O); 9.78 (bs, exchange with D_2O).

*Cis-6,7-dihydroxy-4-phenyl-2-N,N-di-n-propylaminotetralin hydrobromide, **1c***
Compound **1c** was synthetized from **15** in the same manner as **2c** in 78% yield, mp 220–222°C. Anal $C_{22}H_{29}NO_2$. HBr (C, H, N, Br). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ ppm 0.92 (t, 6H); 1.72 (m, 4H); 2.00 (dd, 1H); 2.35 (bd, 1H); 3.04 (m, 4H); 3.22 (m, 2H); 3.78 (m, 1H); 4.07 (dd, 1H); 6.01 (s, 1H); 6.54 (s, 1H); 7.21 (d, 2H); 7.26 (t, 1H); 7.35 (dd, 2H).

*1-(3,4-Dimethoxyphenyl)-4-hydroxy-4-(4-methoxyphenyl)-butan-2-one, **18***
A solution of diisopropylamine (14 ml, 100 mmol) in THF (75 ml) was treated with n-BuLi (1.5 M in *n*-hexane, 66 ml, 100 mmol), at 0°C, under nitrogen, with stirring. After 30 min, the solution was cooled to –78°C. A solution of 3,4-dimethoxy-phenyl-2-propanone, 4 (14.4 g, 74 mmol) in THF (75 ml) was slowly added, and after a few minutes a solution of 3,4-dimethoxybenzaldehyde (10 g, 74 mmol) in THF (75 ml) was added dropwise while keeping the temperature at –78°C. After 3 h at the same temperature, the mixture was poured into water (500 ml) and the product was extracted with ethyl acetate (300 ml x 3).

The extracts were washed with water, dried (Na_2SO_4) and evaporated. The crude mixture was chromatographed on a silica gel column, with a mixture of methylene chloride/methanol, 98:2 as the eluent, to give 13 g (53%) of 18, mp 61–63°C. ^{1}H-NMR ($CDCl_3$ 300 MHz): δ ppm 2.80 (dd, 1H); 2.90 (dd, 1H); 3.64 (s, 2H); 3.79 (s, 3H); 3.85 (s, 3H); 3.87 (s, 3H); 5.07 (dd, 1H); 6.65 (d, 1H); 6.71 (dd, 1H); 6.81 (d, 1H); 6.85 (d, 2H); 7.22 (d, 2H).

*6,7-Dimethoxy-4-(4-methoxyphenyl)-2-tetralone, **19***
Compound **19** was synthetized from **18** (24.2 mmol) in the same manner as **6** giving 6.8 g of crude **19** which was used immediately for the next step without further purification.

*Cis-6,7-dimelhoxy-4-(4-methoxyphenyl)-2-hydroxytetralin, **20***
Compound **20** was synthetized from **19** in the same manner as **7** giving 2.8 g (37%) of **20**. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ ppm 1.88 (dt, 1H); 2.37 (m, 1H); 2.84 (dd, 1H); 3.07 (ddd, 1H); 3.62 (s, 3H); 3.82 (s, 3H); 3.84 (s, 3H); 4.11 (dd, 1H); 4.21 (m, 1H); 6.22 (s, 1H); 6.57 (s, 1H); 6.84 (d, 2H); 6.97 (d, 2H).

*Cis-6,7-dimethoxy-4-(4-methoxyphenyl)-2-methanesulphonyl-oxytetralin, **21***
Compound **21** was obtained from **20** in the same way as **8** giving 2.8 g (90%) of **21**, mp 134–135°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ ppm 2.07 (q, 1H); 2.55 (m, 1H); 3.02 (s, 3H); 3.14 (dd, 1H); 3.27 (ddd, 1H); 3.60 (s, 3H); 3.81 (s, 3H); 3.85 (s, 3H); 4.12 (dd, 1H); 5.11 (m, 1H); 6.24 (s, 1H); 6.58 (s, 1H); 6.85 (d, 2H); 7.06 (d, 2H).

*Trans-6,7-dimethoxy-4-(4-methoxyphenyl)-2-aminotetralin hydrochloride, **22***
Compound **22** was synthetized from **21** in the same manner as **12** giving 1.7 g (84%) of **22** as colourless oil. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ ppm 2.20–2.50 (m, 2H); 3.04 (dd, 1H); 3.30 (dd, 1H); 3.53 (m, 1H); 3.70 (s, 3H); 3.75 (s, 3H), 3.83 (s, 3H); 4.26 (t, 1H); 6.40 (s, 1H); 6.61 (s, 1H); 6.76 (d, 2H); 6.83 (d, 2H); 8.35 (bs, exchange with D_2O).

*Trans-6,7-dihydroxy-4-(4-hydroxyphenyl)-2-aminotetralin hydrobromide, **23***
Boron tribromide (1.5 ml, 16.2 mmol) in dry dichloromethane (15 ml) was added, at 0°C, to a solution of **22** (1.7 g, 5.4 mmol) in dry dichloromethane (25 ml). The mixture was stirred for 3 h

at room temperature, then the solvent was evaporated and the residue was dissolved in ethanol (50 ml) and the solvent was removed again. The residue was dissolved in ethanol-ethyl acetate 1:1 (50 ml). The solution was treated with activated charcoal and filtered. The solvents were removed under reduced pressure and the residue was taken up with ethyl acetate. A grey precipitate was collected by filtration, giving 1.4 g (73%) of **23** as an amorphous solid. Anal $C_{16}H_{17}NO_3$. HBr (C, H, N, Br). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ ppm 2.03 (m, 2H); 2.64 (dd, 1H); 3.00 (dd, 1H); 3.28 (m, 1H); 4.08 (t, 1H); 6.24 (s, 1H); 6.54 (s, 1H); 6.67 (d, 2H); 6.78 (d, 2H); 7.95 (bs, exchange with D_2O); 8.75 (bs, exchange with D_2O).

*5,6-Dimethoxy-3-phenylindan-1-one, **26***
A well stirred solution of cinnamic acid, **25** (78 g, 526 mmol), and veratrole, **24** (69 g, 499 mmol) in polyphosphoric acid (4.15 g) was heated at 95°C for 4 h. After cooling, the solution was diluted with water (500 ml) and extracted with toluene (500 ml x 2). The extract was washed with NaOH 2N (200 ml) and water (500 ml), dried (Na_2SO_4) and evaporated. Crystallization from ethanol gave 99 g of **26** (74%) as white crystals, mp 105–107°C. ^{1}H-NMR ($CDCl_3$, 300MHz): δ ppm 2.62 (dd, 1H); 3.20 (dd, 1H); 3.82 (s, 3H); 3.92 (s, 3H); 4.57 (dd, 1H); 6.63 (s, 1H); 7.11–7.32 (m, 6H aromatics).

*5,6-dimethoxy-3-phenyl-1-oxime-indan, **27***
A mixture of **26** (5.7 g, 21 mmol), hydroxylamine hydrochloride (5.5 g, 79 mmol) and potassium carbonate (5.5 g, 40 mmol) in methanol (160 ml) and water (1.6 ml) was stirred at reflux for 2 h. After cooling the solution was poured on crushed ice. The product was collected by filtration and crystallized from ethanol to give 4.28 g (72%) of **27**, mp 160–163°C. ^{1}H-NMR (DMSO-d_6, 300 MHz): δ ppm 2.62 (dd, 1H); 3.32 (dd, 1H); 3.37 (s, exchange); 3.63 (s, 3H); 3.80 (s, 3H); 4.42 (dd, 1H); 6.58 (s, 1H); 7.08–7.31 (m, 6H). MS m/e 283.

*5,6-Dimethoxy 3-phenyl-(p-toluensulphonyloxime)-indan, **28***
p-Toluensulphonyl chloride (6.3 g, 33 mmol) in pyridine (10 ml) was added dropwise at room temperature to a stirred solution of **27** (4.95 g, 17 mmol) in pyridine (20 ml). After 5 h the solution was poured into water (200 ml) and the product was collected by filtration, washed with water and crystallized with toluene (40 ml) to give 6 g (78%) of **28**, mp 138–140°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ ppm 2.45 (s, 3H); 2.87 (dd, 1H); 3.55 (dd, 1H); 3.87 (s. 3H); 3.91 (s, 3H); 4.37 (dd, 1H); 6.50 (s, 1H); 7.02 (bd, 2H); 7.12 (s, 1H); 7. 26 (m, 3H); 7.35 (d, 2H); 8.13 (d, 2H).

*5,6-Dimethoxy-3-phenyl-2-amino-1-indanone, **29***
A solution of sodium (0.79 g, 34.3 mmol) in ethanol (35 ml) was added to a suspension of **28** (5.65 g, 12.9 mmol) in toluene (50 ml) in a nitrogen atmosphere at room temperature. The mixture was stirred for 3 h, then petroleum ether (30–70°C, 20 ml) was added; the solid was filtered off and the solution was made slightly acidic with hydrochloric acid. The solution was heated at 40°C for 2 h, then the solvent was evaporated under reduced pressure. The residue was taken up in ethyl acetate to give 3.13 g (76%) of **29**. ^{1}H-NMR (DMSO-d_6, 300 MHz): δ ppm 3.71 (s, 3H); 3.85 (s, 3H); 4.16 (d, 1H); 6.56 (s, 1H); 7.25 (s, 1H); 7.38 (m, 5H); 9.10 (bs, exchange with D_2O).

*5,6-Dimethoxy-3-phenyl-2-amino-1-hydroxy-indan, **30***
The indanone **29** (3.13 g, 9.7 mmol) dissolved in methanol (50 ml) and water (10 ml) was reduced with $NaBH_4$ (0.76 g, 20 mmol). After 16 h at room temperature, the solution was acidified with sulphuric acid. Methanol was evaporated under reduced pressure and ammonium hydroxide was added to the residue. Chloroform extraction and evaporation of the extract gave an oil which crystallized from ethyl acetate, yielding 1.97 g (71%) of the alcohol 30, mp 180–181°C. ^{1}H-NMR (DMSO-d_6, 300 MHz): δ ppm 3.05 (dd, 1H); 3.56 (s, 3H); 3.68 (d, 1H); 3.77 (s, 3H); 4.58 (bd, 1H); 6.24 (s, 1H); 6.90 (s, 1H); 7.18-7.38 (m, 5H). MS m/e: 285.

*Trans-5,6-dimethoxy-1-phenyl-2-amino-indan, **31***
The alcohol **30** (10 g, 35 mmol) dissolved in ethanol (50 ml) was treated with 35% hydrochloric acid (1 ml) and hydrogenated in a Parr apparatus with palladium on activated charcoal at 40 psi and at 60°C. After absorption of the theoretical volume of hydrogen, the catalyst was filtered off and the solvent evaporated. The residue was crystallized from ethyl acetate, giving 8 g (75%) of **31** as the hydrochloride, mp 240°C. ^{1}H-NMR (DMSO-d_6, 300 MHz): δ ppm 2.98 (dd, 1H); 3.36 (dd, 1H); 3.60 (s, 3H); 3.76 (s, 3H); 3.81 (m, 1H); 4.52 (d, 1H); 6.48 (s, 1H); 6.99 (s, 1H); 7.18 (d, 2H); 7.27 (t, 1H); 7.34 (t, 2H). MS, m/e: 269.

*Trans-5,6-dihydroxy-1-phenyl-2-aminoindan hydrobromide, **3a***
A solution of **31** (3 g, 9.8 mmol) in 40% hydrobromic acid (35 ml) was refluxed for 3 h. After cooling, ethanol was added (100 ml) and the mixture evaporated under reduced pressure. The residue was crystallized from ethanol (100 ml), giving 8 g of **3a** (88%); mp 258–260°C. Anal $C_{15}H_{15}NO_2$. HBr (C, H, N, Br). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ ppm 2.84 (dd, 1H); 3.27 (dd, 1H); 3.86 (ddd, 1H); 4.28 (d, 1H); 6.2 (s, 1H); 6.72 (s, 1H); 7.17 (d, 2H); 7.28 (t, 1H); 7.35 (t, 2H); 8.27 (bs, exchange with D_2O); 8.78 (bs, exchange with D_2O); 8.83 (bs, exchange with D_2O). MS m/e: 241.

*Trans-6,7-dimethoxy-2-(N,N-dimethyl-amino)-l-phenyl-indan, **32***
A solution of **31** (22 g, 72 mmol), sodium formiate (5.1 g, 75 mmol), formic acid 88% (15 ml) and formaldehyde 32% (32 ml) in DMF (100 ml) was heated for 3 h at 110°C. After cooling and evaporation of the solvent under reduced pressure, water (200 ml) was added and the pH was made alkaline with sodium hydroxide, then the solution was extracted with dichloromethane (2 x 100 ml). The combined extracts were dried (Na_2SO_4) and evaporated. The residue was converted to the hydrochloride salt and crystallized from ethyl acetate to give 20.6 g of **32** (85%), mp 88–90°C. ^{1}H-NMR (DMSO-d_6, 300 MHz): δ ppm 2.58 (d, 3H); 2.68 (d, 3H); 3.32 (d, 1H); 3.41 (dd, 1H); 3.56 (s, 3H); 3.76 (s, 3H); 4.17 (m, 1H); 4.82 (d, 1H); 6.32 (s, 1H); 6.93 (s, 1H); 7.27 (m, 3H); 7.36 (t, 2H). MS, m/e: 297.

*Trans-5,6-dihydroxy-2-(N,N-dimethylamino)-1-phenylindan hydrobromide, **3b***
Compound **3b** (3.4 g, 10.1 mmol) was obtained in the same way as **3a**, yield 77% as crystals from ethanol, mp 215–217°C. Anal $C_{17}H_{19}NO_2$·HBr (C, H, N, Br). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ ppm 2.71 (bs, 6H); 3.15 (dd, 1H); 3.33 (dd, 1H); 4.24 (ddd, 1H); 4.60 (d, 1H); 6.11 (s, 1H); 6.69 (s, 1H); 7.24 (d, 2H); 7.28 (t, 1H); 7.37 (t, 2H); 8.80 (s, 1H, exchange D_2O); 8.88 (s, 1H, exchange with D_2O). MS, m/e: 269.

*Trans-5,6-dihydroxy-1-phenyl-2-(N,N-di-n-propyl)aminoindan hydrobromide, **3c***
Compound **3c** was obtained from **32** in the same manner as **2c**. Starting from 49% yield as white crystals (from ethyl acetate), mp 170–172°C. Anal $C_{21}H_{27}NO_2$. HBr (C, H, N, Br). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ ppm 0.54 (t, 3H); 0.85 (t, 3H); 1.30–1.75 (m, 4H); 2.85-3.10 (m, 4H); 3.20 (dd, 1H); 3.40 (dd,

1H); 4.41 (ddd, 1H); 4.64 (d, lH); 6.02 (s, 1H); 6.67 (s, 1H); 7.25–7.42 (m, 5H); 8.79 (s, lH; exchange with D_2O); 8.85 (s, 1H, exchange with D_2O); 9.11 (bs, lH, exchange with D_2O).

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