

Stereospecific and Selective 5-HT₂ Antagonism in a Series of 5-Substituted *trans*-1-Piperazino-3-phenylindans

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A study of the effect of aromatic substitution on 5-HT₂, D₂, and α₁ receptor affinity in a subseries of new and previously synthesized 1-piperazino-3-phenylindans indicated that high 5-HT₂ selectivity could be obtained in 5-substituted derivatives. Accordingly, a series of 5-substituted derivatives was synthesized with the goal of obtaining stereospecific and selective, centrally acting 5-HT₂ antagonists. This goal was fulfilled in 5-chloro- or 5-fluoro-substituted compounds with 2-(3-alkyl-2-oxoimidazolidin-1-yl)ethyl- or 2-(tetrahydro-2-oxo-1*H*-pyrimidin-1-yl)ethylpiperazine substituents, as well as in their imidazolidine-2-thione or pyrimidine-2-thione analogues. The most interesting derivatives were resolved either directly via diastereomeric salts or by syntheses from resolved starting materials. Optical purity was determined by a ¹H NMR method, using the chiral shift reagent (*R*)-(-)-2,2,2-trifluoro-1-(9-anthryl)ethanol. The compound (-)-*trans*-1-[2-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]-3-isopropyl-2-imidazolidinone ((-)-20) had the overall best profile with a high stereoselectivity (eudismic ratio: 68) and a high selectivity versus D₂ and α₁ receptors (affinity ratios 182 and 191, respectively). It had a potent central effect but was shorter-acting than the tetrahydropyrimidinone or thione derivatives ((-)-39, (+)-40, (-)-41, and (+)-42). The observed activities of the compounds are settled in perspective in relation to a recently proposed D₂ receptor interaction model. While there are no indications so far that *trans*-1-piperazino-3-phenylindans interact with D₂ and 5-HT₂ receptors in different conformations, the present study shows important differences in aromatic substitution effects. Only 5-HT₂ receptors are able to accommodate a 5-substituent in the indan benzene ring, thus allowing syntheses of highly selective compounds.

Some years ago we reported the structure-activity relationships of a series of antihypertensive *trans*-1-piperazino-3-phenylindans.¹ These compounds had high affinity for serotonin₂ (5-HT₂) receptors and were potent antagonists of the 5-HT-induced pressor effect in pithed rats. From this series (1*R*,3*S*)-1-[2-[4-[2,3-dihydro-3-(4-fluorophenyl)-1*H*-inden-1-yl]-1-piperazinyl]ethyl]-2-imidazolidinone (1, irindalone, Figure 1) was selected as a promising antihypertensive compound.^{1,2} The central 5-HT₂ antagonistic effect (antagonism of *l*-5-HTP-induced head twitches) of these compounds were generally much lower than their peripheral effect. A few derivatives had potent central effects but had rather low selectivity with regard to dopamine (DA) D₂ receptors and α₁ adrenoceptors.¹

Centrally acting 5-HT₂ antagonists have shown promising effects in animal models for anxiety³ and depression⁴ as well as in certain drug-abuse models.⁵⁻⁷ Clinical investigations with the 5-HT₂ antagonist ritanserin have demonstrated efficacy in anxiety,⁸ dysthymic disorder,⁹ and improvement of sleep quality in dysthymic patients (increase of slow wave sleep).¹⁰ In schizophrenic patients improvements of negative symptoms¹¹ and extrapyramidal symptoms¹²⁻¹⁴ have been demonstrated. A prophylactic effect of 5-HT₂ antagonists against migraine has also been hypothesized, but clinical evidence is lacking. It has been argued that it might rather be 5-HT_{1C} receptors that are involved in the triggering of migraine attacks.¹⁵

The cloning and sequencing of 5-HT receptors have revealed a high homology between 5-HT₂ and 5-HT_{1C} receptors, and they share the same second messenger system (phosphoinositide hydrolysis).^{16,17} Phylogenetic

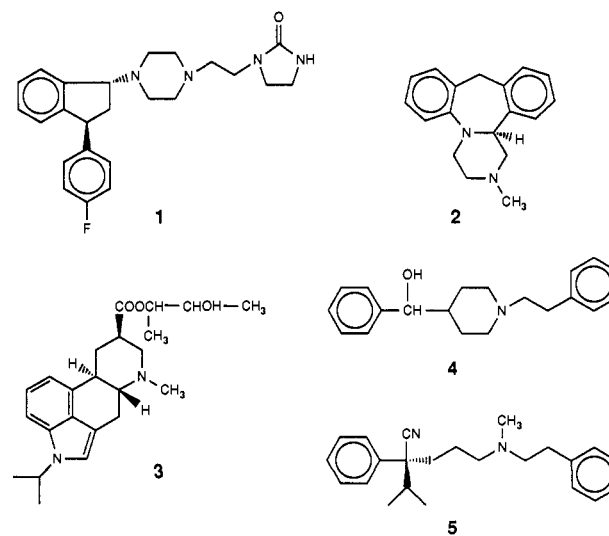


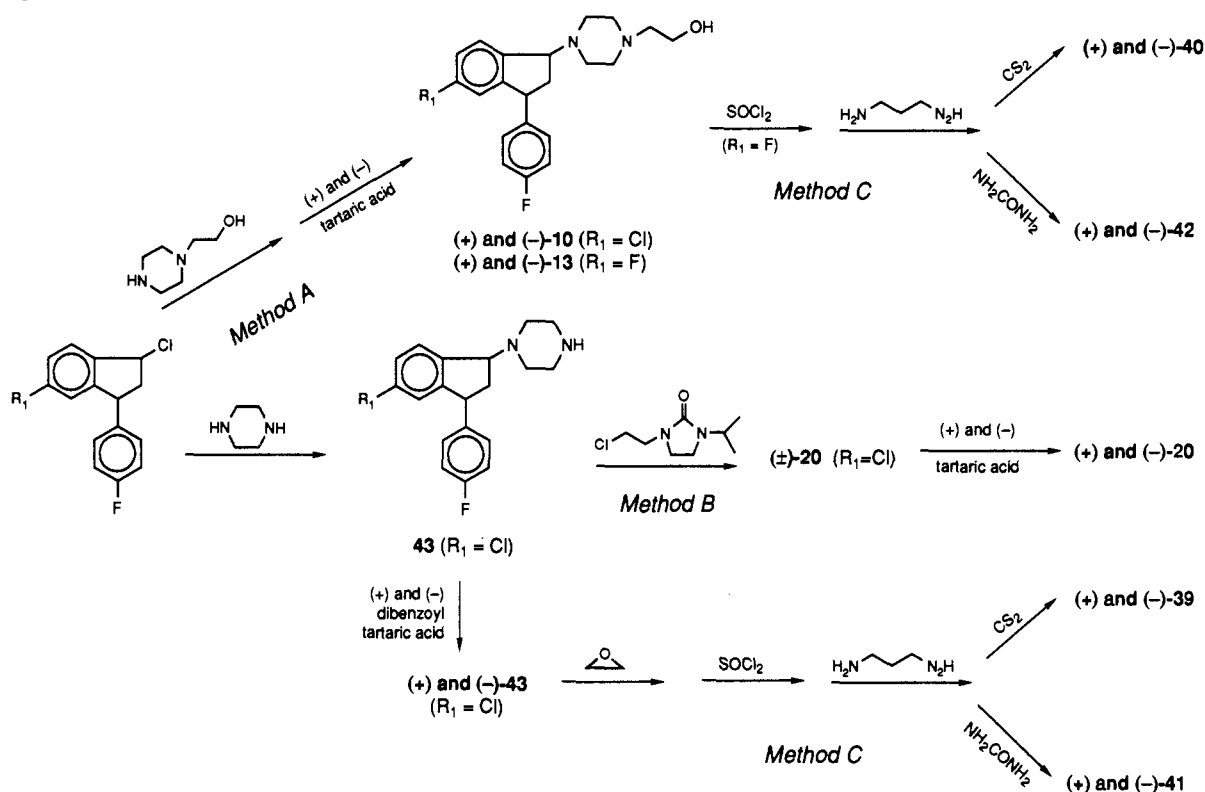
Figure 1. Structures of chiral 5-HT₂ antagonists.

analysis confirms that these two subtypes belong to the same "branch" of the G-protein coupled 5-HT receptors.¹⁸ Numerous binding studies show that many agents with affinity for 5-HT₂ receptors also have high affinity for 5-HT_{1C} receptors (e.g., ritanserin has high affinity for both subtypes).¹⁹ While 5-HT₂ antagonists such as ketanserin and MDL 11939²⁰ (4, Figure 1) show moderate to high selectivity for 5-HT₂ receptors versus 5-HT_{1C} receptors, no selective 5-HT_{1C} antagonist has yet been described.¹⁹

Both in pharmacological and biochemical studies in animals as well as in certain studies in humans (e.g., various scanning methods such as PET studies) enantiomers displaying a high stereoselectivity toward a certain receptor are of considerable interest. The enantiomers of unse-

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Scheme I



lective 5-HT₂ antagonists, such as methiothepine²¹ or octoclothepeine,²² have equal, high affinity for the 5-HT₂ receptor. The (*S*)-(+)-enantiomer of the antidepressant mianserin (**2**) has only 4–5 times higher affinity for serotonin receptors than its corresponding (*R*)-enantiomer (³H-mianserin binding).^{23,24}

1-Isopropyl-substituted ergolines, such as LY53857²⁵ (**3**), its corresponding 8-(4-methoxycyclohexyl) ester, sergolexole,²⁶ and the *N*-cyclohexyl-8-carboxamide analogue, LY237733,²⁷ are all potent and selective 5-HT₂ antagonists with respect to D₂ receptors and α_1 adrenoceptors. However, LY237733 has similar affinity for 5-HT₂ and 5-HT_{1C} receptors.²⁷ While it has been reported that the four side chain stereoisomers of **3** have similar 5-HT₂ receptor affinity,²⁸ there is no information in the literature concerning 5-HT₂ receptor affinities of ergolines with simultaneous opposite configuration of the hydrogens in both the 5 and 10 positions. Such information would be valuable in relation to receptor modeling.

The enantiomers of **4** show a rather low stereoselectivity (eudismic ratio²⁹ of 9).³¹ The mixed calcium antagonist/5-HT₂ antagonist (*S*)-emopamil (**5**) has a 13 times higher affinity for the 5-HT₂ receptor than its corresponding (*R*)-enantiomer.³²

The eudismic ratio for **1** and its corresponding (1*S*,3*R*)-enantiomer was as high as 168.¹ However, although **1** displayed a more than 100-fold selectivity for 5-HT₂ versus D₂ receptors, the selectivity versus α_1 adrenoceptors was only 8-fold. The enantiomers of the neuroleptic "parent" of **1**, tefludazine, also showed a high stereoselectivity for 5-HT₂ receptors.³³ However, like other 6-substituted *trans*-1-piperazino-3-phenylindans³⁴ the active enantiomer had also high affinity for D₂ receptors and α_1 adrenoceptors. We therefore decided to continue our studies of the structure-activity relationships of 1-piperazino-3-phenylindans with the goal of obtaining compounds with (1) potent central 5-HT₂ antagonistic activity, (2) high se-

lectivity versus D₂ receptors and α_1 adrenoceptors, and (3) high stereoselectivity toward 5-HT₂ receptors. In this paper we report 5-HT₂ affinity and 5-HT₂ antagonism in vivo of a new series of 5-substituted compounds as well as of certain compounds which we previously have examined for D₂ antagonistic effects.^{34,35}

Chemistry

The *trans*-1-piperazino-3-phenylindan derivatives presented in Tables IV-VII were all prepared by methods previously reported,^{1,34} i.e., by alkylation of a 1-substituted piperazine derivative with a suitable substituted 1-chloro-3-phenylindan (method A, Scheme I), by alkylating a substituted 1-(3-phenyl-1-indanyl)piperazine with a chloroalkyl-substituted heterocyclic compound (method B, Scheme I), or by constructing the heterocyclic ring in a three-step reaction starting with the piperazine ethanol derivatives **10** or **13** or their enantiomers (method C).

As usual, the 1-chloro-3-phenylindans were obtained from the corresponding *cis*-3-phenylindan-1-ols (**8a-n**, Tables I and II) upon treatment with thionyl chloride in a suitable solvent, such as ether or dichloromethane.^{1,34} The 3-phenylindan-1-ols were obtained by reduction of the corresponding 3-phenylindan-1-ones (**7a-n**, Tables I and II) with sodium borohydride.^{1,34} 3-Phenylindan-1-ones, not previously reported, were obtained from the corresponding 1-amino-3-cyano-2-(methoxycarbonyl)-3-phenyl-1*H*-indenes (**6a-n**, Tables I and II) produced by a method we have published recently.³⁶ This method allows introduction of aromatic substituents in positions inaccessible by previously reported methods for preparation of 3-phenylindan-1-ones.^{34,37}

The different strategies used to obtain the enantiomers of selected compounds are shown in Scheme I. Compounds **10**, **13**, and **20** were resolved directly via their diastereomeric L-(+)- and D-(-)-tartrates. However, attempts to

Table I. Aromatic Substitution Pattern in 1-Aminoindenes (6), 1-Indanones (7), and 1-Indanols (8)

6a-n			7a-n		8a-n	
type	R ₁	R ₂	type	R ₁	R ₂	
a	4-Cl	4-F	h	5-CH ₃	4-F	
b	5-Cl	4-F	i	5-SCH ₃	4-F	
c	6-Cl	4-F	j	5-Cl	H	
d	7-Cl	4-F	k	5-Cl	2-F	
e	5-F	4-F	l	5-Cl	3-F	
f	5-CF ₃	4-F	m	5-Cl	4-Cl	
g	5-Br	4-F	n	5-Cl	4-CH ₃	

Table II. Physicalchemical Data of New 1-Aminoindenes (6), 1-Indanones (7), and 1-Indanols (8)^a

compd ^b	mp, °C	recrystn solv ^c	yield (%)	formula ^d
6h	215-217	IPE	48	C ₁₈ H ₁₆ FN ₂ O ₂
6j	192-194	T	46	C ₁₈ H ₁₅ ClN ₂ O ₂
6k	227-228	D/EA	31	C ₁₈ H ₁₂ ClFN ₂ O ₂
6l	192-193	IPE	52	C ₁₈ H ₁₂ ClFN ₂ O ₂
6m	213-215	T	35	C ₁₈ H ₁₂ Cl ₂ N ₂ O ₂
6n	228-230	DMF/H ₂ O	63	C ₁₈ H ₁₅ ClN ₂ O ₂
7a	74-76	C	61	C ₁₈ H ₁₀ ClFO
7b	84-86	IPE/H	92	C ₁₈ H ₁₀ ClFO
7d	113-116	not recryst	79	C ₁₈ H ₁₀ ClFO
7f	105-106	IPE	81	C ₁₈ H ₁₀ F ₄ O
7g	117-119	IPE	77	C ₁₈ H ₁₀ BrFO
7h	69-71	IPE	63	C ₁₈ H ₁₃ FO
7i ^e	74-76	IPE	43	C ₁₈ H ₁₃ FOS
7j	127-129	IPE	64	C ₁₈ H ₁₁ ClO
7k	83-85	P	46	C ₁₈ H ₁₀ ClFO
7l	118-119	IPE	64	C ₁₈ H ₁₀ ClFO
7m	140-142	H	77	C ₁₈ H ₁₀ Cl ₂ O
7n	112-114	H	82	C ₁₈ H ₁₃ ClO
8a	107-109	C	65	C ₁₈ H ₁₂ ClFO
8b	92-93	C	44	C ₁₈ H ₁₂ ClFO
8d	102-104	C	79	C ₁₈ H ₁₂ ClFO
8f	81-83	P	97	C ₁₈ H ₁₂ F ₄ O
8g	107-109	IPE/P	82	C ₁₈ H ₁₂ BrFO
8h	100-102	IPE/P	89	C ₁₈ H ₁₆ FO
8i	114-116	IPE/EA	83	C ₁₈ H ₁₆ FOS
8j	110-111	IPE/EA	83	C ₁₈ H ₁₃ ClO
8k	78-80	IPE/P	85	C ₁₈ H ₁₂ ClFO
8l	110-112	P	84	C ₁₈ H ₁₂ ClFO
8m	129-131	H	85	C ₁₈ H ₁₂ Cl ₂ O
8n	oil			C ₁₈ H ₁₅ ClO

^a Data for compounds not included in the table have previously been reported in ref 34 (7c, 8c, 7e, 8e) and 35 (6a, 6b, 6f, 6g). ^b See Table I for substitution pattern. ^c C = cyclohexane, D = dichloromethane, DMF = dimethylformamide, EA = ethyl acetate, H = heptane, IPE = isopropyl ether, P = pentane, T = toluene. ^d Anal. C, H, N. ^e Prepared by cyclization of the corresponding 4-F-3'-CH₃S-substituted diphenylpropionic acid with polyphosphoric acid.³⁴

resolve 39 and 40 directly via diastereomeric salts with chiral acids were unsuccessful. The enantiomers of the 5-fluoro derivative 40 were instead prepared from the pure enantiomers of 13 by the reaction sequence shown in Scheme 1. By substituting carbon disulfide with urea in the last step of method C the enantiomeric pair (+)-42 and (-)-42 was also prepared directly from the pure enantiomers of 13.

The method for the direct resolution of compound 10 proved to be inapplicable for preparation of larger quantities of the enantiomers. In contrast, it was easy to

Table III. Optical Purity and ¹H NMR Chemical Shifts of H₃ of Resolved Compounds

compd	δ H ₃ ^a (ppm)	Δδ H ₃ ^b (ppm)	optical purity (%)
(+)-10	4.40	0.08	98.7
(-)-10	4.40	0.16	98.7
(+)-13	4.40	0.19	≥99.5
(-)-13	4.40	0.08	98.7
(+)-20	4.39	0.09	≥99.4
(-)-20	4.39	0.17	≥99.5
(+)-39	4.39	0.10	≥99.2
(-)-39	4.39	0.16	≥99.4
(+)-41	4.39	0.09	≥99.4
(-)-41	4.39	0.16	99.0

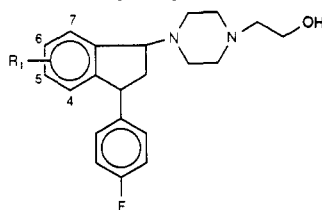
^a Chemical shift value without (R)-2,2,2-trifluoro-1-(9-anthryl)-ethanol. ^b Upfield chemical shift displacement induced by addition of 2 equiv of (R)-2,2,2-trifluoro-1-(9-anthryl)ethanol.

scale up the resolution of the corresponding nor-derivative 43 (Scheme 1). Treatment of the enantiomers of 43 with ethylene oxide afforded the enantiomers of 10 in an alternative way. The enantiomers of 39 and 41 were subsequently prepared in the same manner as the enantiomers of 40 and 42.

The optical purity of the resolved compounds was determined by ¹H NMR spectroscopy on mixtures of the enantiomers and the chiral shift reagent (R)-(-)-2,2,2-trifluoro-1-(9-anthryl)ethanol. The methodology was similar to what we have recently described for the determination of optical purity of the octoclothepein enantiomers.²² The chemical shift of H₃ (assigned by long-range coupling to H₄ in the indan ring system and the H₂ in the 4-fluorophenyl ring in the 2D COSY spectrum of 10; see figure in Table III) proved to be very sensitive toward the influence of the shift reagent and could be studied without problems with overlapping signals. The chemical shift values of H₃ with and without addition of 2 equiv of the shift reagent are listed in Table III together with the estimated optical purity. The optical purity was calculated from the peak heights of the central peak in the H₃ triplets, assuming that the line shape of this signal was identical for the two enantiomers. When no signals from the opposite enantiomer could be detected, the purity estimation was limited to the signal to noise ratio. As mentioned, the enantiomers of 40 and 42 were prepared from the enantiomers of 13 by chemical reactions that did not involve the chiral atoms. The chemical purity of the (+)- and (-)-enantiomers of 40 and 42 must therefore be at least as high as the optical purities of (+)-13 and (-)-13, respectively.

The absolute configuration of 1 is 1R,3S.¹ Comparison of the CD-spectra of 1 with other resolved D₂ and/or 5-HT₂ antagonists from the *trans*-1-piperazino-3-phenylindan class of compounds have invariably shown that the more potent enantiomer has the 1R,3S configuration.^{1,33} Therefore, we assume that the configuration of the eutomers of the resolved compounds in this series also have the 1R,3S configuration.

The sign of the optical rotation is *not* generally indicative of the absolute configuration. Within D₂/5-HT₂-antagonistic *trans*-1-piperazino-3-phenylindans we have ob-

Table IV. Aromatic Substitution Effects in a Series of *N*-(2-Hydroxyethyl)-Substituted *trans*-1-Piperazino-3-phenylindans^a

compd ^b	R ₁	mp (°C)	formula ^c	receptor binding ^d			quipazine inhibition (rats) ^e
				5-HT ₂	D ₂	α ₁	
9	4-Cl	<i>f</i>	<i>f</i>	40	220	30	0.82 (0.18–3.7)
10	5-Cl	267–270	C ₂₁ H ₂₄ ClFN ₂ O·2HCl	25	2200	230	0.23 (0.066–0.81)
(+)-10	5-Cl	224–227	C ₂₁ H ₂₄ ClFN ₂ O·2HCl	230	6300	2500	>2.8
(-)-10	5-Cl	224–227	C ₂₁ H ₂₄ ClFN ₂ O·2HCl	11	370	210	0.86 (0.45–1.7)
11	6-Cl	<i>g</i>	<i>g</i>	2.6	20	26	0.039 (0.014–0.11)
12	7-Cl	140–142	C ₂₁ H ₂₄ ClFN ₂ O-dimaleate	15	46	38	1.3 (0.30–5.7)
13	5-F	<i>g</i>	<i>g</i>	21	1100	150	0.35 (0.08–1.5)
(+)-13	5-F	224–226	C ₂₁ H ₂₄ F ₂ N ₂ O·2HCl	12	330	72	0.33 (0.11–1.0)
(-)-13	5-F	223–226	C ₂₁ H ₂₄ F ₂ N ₂ O·2HCl	500	22000	1100	>2.8
14	5-CF ₃	172–174	C ₂₂ H ₂₄ F ₄ N ₂ O-dimaleate	8.9	1300	380	1.0 (0.27–3.7)
15	5-CH ₃	169–171	C ₂₂ H ₂₇ FN ₂ O-dimaleate	12	1100	270	>2.1

^a Isomeric purity: >95% *trans*-isomer (TLC). ^b All compounds were made by method A (Scheme I). ^c Anal. C, H, N. ^d Results are expressed as IC₅₀ values in nM and are the logarithmic mean of at least two determinations. Two full concentration effect curves were measured using five concentrations of the test drug in triplicate (covering three decades). Sd-ratios were obtained by calculating the variance of repeated measures of ratios between the first and the second IC₅₀ determination for a series of 100 drugs. In the cases of ratios greater than 3 times the sd (99% confidence interval) extra determinations were performed and the outliers were discarded. The following 95% confidence ratios (2 times sd-ratio) were calculated: D₂, 2.25; α₁, 2.20; 5-HT₂, 2.05. ^e Results are expressed as ED₅₀ values in μmol/kg (sc); 95% confidence limits in parentheses. ^f See ref 35. ^g See ref 34.

served that the active enantiomers are dextrorotatory with the exception of compounds substituted with chlorine in the indan benzene ring. From the present series it also appears that chlorine-substituted eutomers are levorotatory.

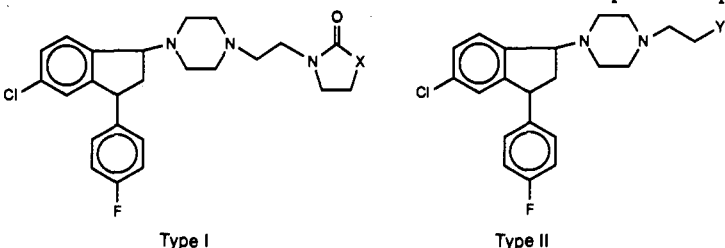
Results and Discussion

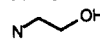
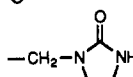
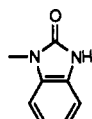
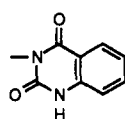
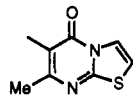
Details concerning the test methods are described in the Experimental Section. Affinities for brain 5-HT₂ receptors, D₂ receptors and α₁ adrenoceptors of all compounds are shown in Tables IV–VII. Antagonism of the characteristic head-twitch syndrome, induced by the 5-HT₂ agonist quipazine, was used as a measure of central 5-HT₂ antagonistic activity. This effect was measured for most compounds and is also shown in the tables. Antagonistic effect after 24 h was measured for selected compounds (Table VIII) as well as inhibition of pergolide-induced rotations in rats with unilateral 6-hydroxydopamine (6-OHDA) lesions. Data for the reference compounds 1 and ritanserin (44) are given in Tables VII and VIII.

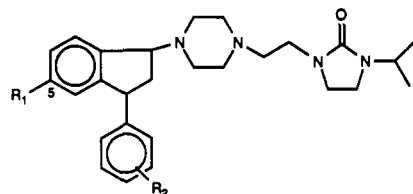
In Table IV is shown a series of *N*-(2-hydroxyethyl)-substituted compounds. We have previously shown that the 5-fluoro-substituted derivative 13 was very weak or inactive in neuroleptic test models reflecting in vivo D₂ antagonism.³⁴ More recently, the effect of aromatic substitution on D₂ affinity was investigated in a series of 1-piperazino-3-phenylindans and corresponding 10-piperazino-10,11-dihydrobenzo[*b,f*]thiepins.³⁵ Here the very low D₂ affinity of 10 was reported. However, in connection with the structure–activity study of 1 and its derivatives, we made a superimposition study of 1 and the prototype 5-HT₂ antagonist ketanserin.¹ Inspection of this preliminary 5-HT₂ receptor interaction model showed that the position of the fluoro atom in ketanserin was coincident with the 5-position of the indan ring system of 1. This observation initiated testing of 10 and 13 for 5-HT₂ activity, and as can be seen from Table IV, these compounds indeed

had significant 5-HT₂ affinity and 5-HT₂-antagonistic activity in vivo. Interestingly, these two compounds had very low α₁ affinity compared with 1 (Table VII) and its analogues.¹ A similar selective profile was found for the 5-CF₃- and the 5-CH₃-substituted derivatives 14 and 15, but these compounds were less potent in vivo. Resolution of 10 and 13 revealed that the 5-HT₂-antagonistic effect resided in one of the enantiomers in accordance with what has been observed in compounds which are unsubstituted or 6-substituted in the indan ring system.^{1,33} To complete the investigation of the effect of substitution in different positions of the indan ring we measured the effects of the 4-chloro and the 7-chloro derivatives 9 and 12. Both derivatives had significant 5-HT₂ activity, but the 4-chloro derivative was equally potent on α₁ adrenoceptors and the 7-chloro derivative had both significant D₂ and α₁ affinity. The 6-chloro derivative 11 is a potent neuroleptic compound,³⁴ but was still the most potent 5-HT₂ antagonist of the compounds in Table IV. The next goal was therefore to obtain equally potent compounds among the seemingly selective 5-substituted compounds.

The study of 1 and its derivatives¹ indicated that 5-HT₂ affinity could be increased by substituting the hydroxyethyl side chain with various heterocyclic side chains. The obvious step was therefore to apply this principle to the 5-substituted derivatives. In Table V is shown a series of 5-chloro-substituted compounds with heterocyclic side chains. Generally, the principle worked very well, giving more potent and still selective 5-HT₂ antagonists. The structure–activity relationships were also parallel to those observed in the derivatives of 1, i.e., increased potency in vivo of compounds alkylated in the N3 position of the imidazolidinone ring (17–19) and lower activity of oxazolidinone derivatives (23) or pyrrolidinone derivatives (22) in comparison with the imidazolidinone derivative 16 (the 5-chloro derivative of 1). Compounds with benzo-fused heterocyclic side chains (25, 26) or “ritanserin side chain” (27) were less potent and/or selective than compounds

Table V. Effect of Side Chain Variations in a Series of 5-Chloro-4'-fluoro-Substituted *trans*-1-Piperazino-3-phenylindans^a


compd ^b	type	X/Y	mp (°C)	formula ^c	receptor binding ^d			quipazine inhibition (rats) ^e
					5-HT ₂	D ₂	α ₁	
16	I	NH	168–170	C ₂₄ H ₂₈ ClFN ₄ O	2.9	360	200	0.34 (0.16–0.71)
17	I	N-Me	164–166	C ₂₅ H ₃₀ ClFN ₄ O-dimaleate	2.8	190	600	0.093 (0.052–0.17)
18	I	N-Et	178–180	C ₂₆ H ₃₂ ClFN ₄ O-dimaleate	2.6	260	240	0.042 (0.0088–0.20)
19	I		168–170	C ₂₈ H ₃₂ ClFN ₄ O ₂ -dimaleate	6.1	320	710	1.1 (0.41–3.0)
20	I	N-iPr	188–190	C ₂₇ H ₃₄ ClFN ₄ O-dimaleate	3.9	280	260	0.060 (0.024–0.15)
(+)-20	I	N-iPr	174.9–175.3	C ₂₇ H ₃₄ ClFN ₄ O-dimaleate	75	1300	340	>7.0
(-)-20	I	N-iPr	175.0–175.3	C ₂₇ H ₃₄ ClFN ₄ O-dimaleate	1.1	200	210	0.031 (0.0079–0.12)
21	I	N-Ph	174–176	C ₃₀ H ₃₂ ClFN ₄ O-dimaleate	44	300	310	>6.7
22	I	CH ₂	250–252	C ₂₅ H ₂₉ ClFN ₃ O·2HCl	10	500	370	2.7 (1.4–5.1)
23/	I	O	244–246	C ₂₄ H ₂₇ ClFN ₃ O ₂ ·2HCl	23	550	140	2.0 (0.57–7.0)
24	II		159–160	C ₂₅ H ₃₀ ClFN ₄ O-dimaleate	10	160	73	0.91 (0.08–10)
25	II		192–194	C ₂₈ H ₂₈ ClFN ₄ O-dimaleate	5.6	110	66	0.21 (0.11–0.41)
26	II		195–198	C ₂₉ H ₂₈ ClFN ₄ O ₂ -dimaleate	3.8	93	78	>3.3
27	II		202–203	C ₂₈ H ₂₈ ClFN ₄ OS-dimaleate	19	65	24	1.9 (0.36–9.9)

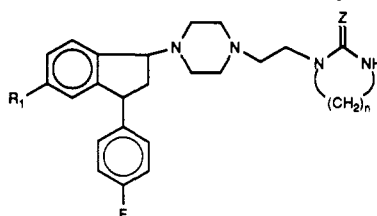
^{a-c} See corresponding footnotes to Table IV. / Isomeric purity: 92% *trans*-isomer.Table VI. Aromatic Substitution Effects in a Series of 3-Isopropyl-2-imidazolidinone-1-(2-ethyl)-Substituted *trans*-1-Piperazino-3-phenylindans^a


compd ^b	R ₁	R ₂	mp (°C)	formula ^c	receptor binding ^d			quipazine inhibition (rats) ^e
					5-HT ₂	D ₂	α ₁	
28	Br	4-F	180–182	C ₂₇ H ₃₄ BrFN ₄ O-dimaleate	6.4	240	270	0.098 (0.022–0.43)
29	CF ₃	4-F	174–176	C ₂₈ H ₃₄ F ₄ N ₄ O-dimaleate	3.7	510	370	0.13 (0.076–0.22)
30	CH ₃	4-F	178–180	C ₂₈ H ₃₇ FN ₄ O-dimaleate	3.0	450	120	0.20 (0.12–0.32)
31	SCH ₃	4-F	140	C ₂₈ H ₃₇ FN ₄ OS·H ₂ O	4.0	720	250	>3.4
32	Cl	H	189–191	C ₂₇ H ₃₅ ClN ₄ O-dimaleate	9.9	750	510	1.0 (0.26–3.9)
33	Cl	2-F	190–192	C ₂₇ H ₃₄ ClFN ₄ O-dimaleate	3.5	920	670	2.1 (0.55–8.0)
34	Cl	3-F	180–182	C ₂₇ H ₃₄ ClFN ₄ O-dimaleate	26	490	970	NT ^f
35	Cl	4-Cl	170–172	C ₂₇ H ₃₄ Cl ₂ N ₄ O-dimaleate	15	280	180	2.9 (0.60–14)
36	Cl	4-CH ₃	184–186	C ₂₈ H ₃₇ ClN ₄ -dimaleate	11	450	60	>3.5

^{a-f} See corresponding footnotes to Table IV. / NT = not tested.

with side chains with monocyclic ring systems. Compounds 17, 18, and 20 were as potent in vivo as the unselective 6-chloro-substituted compound 11. Compound 20 was resolved, and the (-)-enantiomer, (-)-20, proved to be the most potent and selective compound so far.

The next step was to maintain the optimal side chain of 20 and further to investigate aromatic substitution effects in both aromatic rings of the 3-phenylindan ring system. The result of this study is shown in Table VI. In vitro activity was slightly affected in the four derivatives 28–31 with a different 5-substituent. However, in vivo

Table VII. Activity of Selected Compounds with Imidazolidine-2-thione or Tetrahydropyrimidin-2-one or -2-thione Side Chains^a

compd ^b	R ₁	Z	n	mp (°C)	formula ^c	receptor binding ^d			quipazine inhibition (rats) ^e
						5-HT ₂	D ₂	α ₁	
37	Cl	S	1	183–184	C ₂₄ H ₂₆ ClFN ₄ S-dimaleate	1.5	67	52	0.077 (0.027–0.22)
38	F	S	1	172–174	C ₂₄ H ₂₆ F ₂ N ₄ S-dimaleate	1.5	230	110	0.12 (0.044–0.32)
39	Cl	S	2	184–185	C ₂₅ H ₃₀ ClFN ₄ S-dimaleate	1.5	93	170	0.048 (0.019–0.12)
(+)-39	Cl	S	2	212–213	C ₂₅ H ₃₀ ClFN ₄ S·2HCl	21	490	350	NT ^f
(-)-39	Cl	S	2	212–213	C ₂₅ H ₃₀ ClFN ₄ S·2HCl	0.75	33	67	0.041 (0.022–0.078)
40	F	S	2	174–176	C ₂₅ H ₃₀ F ₂ N ₄ S-dimaleate	1.7	220	110	0.039 (0.013–0.11)
(+)-40	F	S	2	205–206	C ₂₅ H ₃₀ F ₂ N ₄ S·2HCl	0.95	140	43	0.017 (0.0063–0.046)
(-)-40	F	S	2	205–206	C ₂₅ H ₃₀ F ₂ N ₄ S·2HCl	42	2900	NT	NT
(+)-41	Cl	O	2	179–180	C ₂₅ H ₃₀ ClFN ₄ O-dimaleate	120	1700	NT	NT
(-)-41	Cl	O	2	179–180	C ₂₅ H ₃₀ ClFN ₄ O-dimaleate	1.3	94	62	0.11 (0.058–0.21)
(+)-42	F	O	2	170–171	C ₂₅ H ₃₀ F ₂ N ₄ O-dimaleate	1.1	280	41	0.029 (0.0091–0.093)
(-)-42	F	O	2	170–171	C ₂₅ H ₃₀ F ₂ N ₄ O-dimaleate	57	4000	NT	NT
1 (irindalone)						3.4	400	2.6	0.58 (0.25–1.3)
44 (ritanserine)						0.40	12	47	0.10 (0.050–0.18)

^{a-c} See corresponding footnotes to Table IV. / NT = not tested.

Table VIII. Inhibition of Quipazine-Induced Head Twitches (2 h and 24 h Pretreatment)^a and Pergolide-Induced Rotation in 6-OHDA-Lesioned Rats (2 h)

compd	pergolide inhibition 2 h	quipazine inhibition	
		2 h	24 h
(-)-20	>14	0.031 (0.0079–0.12)	1.2 (0.24–5.6)
37	>14	0.077 (0.027–0.22)	1.4 (0.21–9.2)
38	>15	0.12 (0.044–0.32)	0.62 (0.26–1.5)
(-)-39	>18	0.041 (0.022–0.078)	0.021 (0.0075–0.059)
(+)-40	>37	0.017 (0.0063–0.046)	0.011 (0.0042–0.029)
(-)-41	>15	0.11 (0.058–0.21)	0.072 (0.023–0.22)
(+)-42	>15	0.029 (0.0091–0.093)	0.070 (0.021–0.23)
1	7.4 (2.8–1.9)	0.58 (0.25–1.3)	0.75 (0.36–1.6)
44	>21	0.10 (0.050–0.18)	0.98 (0.35–2.7)

^a Results are expressed as ED₅₀ values in μmol/kg (sc); 95% confidence limits in parentheses.

compounds 28–30 were slightly less potent than 20, while 31 was inactive. The 2-fluoro analogue of 20, compound 33, was equipotent and more selective in vitro, but in vivo it was a much weaker compound. The unsubstituted analogue and the 3-fluoro, 4-chloro, and 4-methyl analogues of 20 were all less active. The observed substitution effects in the 3-phenyl ring somewhat resemble the effects observed in a similar study of influence of aromatic substitution effects on D₂ affinity.³⁵ Here we found that a 2-fluoro derivative was as potent as the 4-fluoro derivative (in vitro as well as in vivo). The 2-chloro, 3-fluoro, and 4-chloro derivatives were completely inactive, while corresponding derivatives here (34 and 35) retain some activity. In conclusion, none of the compounds in Table VI was superior to 20.

In the study of 1 and its derivatives we observed that compounds with imidazolidine-2-thione or tetrahydropyrimidine-2-thione side chains were more potent 5-HT₂ antagonists, but at the expense of higher antidopaminergic activity.¹ In order to investigate the profile of this derivatives in the present series we prepared the compounds in Table VII, which also include tetrahydropyrimidin-2-one derivatives. Generally, we observed, that all compounds, including the tetrahydropyrimidin-2-ones, were equally or even more potent 5-HT₂ antagonists than 20. However, because D₂ and α₁ affinities were increased

in these compounds, (-)-20 was still the most selective compound with regard to both these receptors. Nevertheless, the active enantiomers of 39–42 are rather selective compounds (D₂/5-HT₂ selectivity ratios from 44 to 250 and α₁/5-HT₂ selectivity ratios from 37 to 89). We also tested the most interesting compounds for antagonistic activity against pergolide-induced circling behavior in rats with unilateral 6-OHDA lesions (Table VIII). This is a very sensitive model for D₂ antagonistic effect in vivo. No effect could be observed for any compound in doses more than 2 orders of magnitude higher than the doses needed to antagonize quipazine-induced head twitches. Also shown in Table VIII are the effects of selected compounds in the quipazine test after 24 h (2 h values are shown for comparison). The active enantiomers of 39–42 are more potent than (-)-20, and the enantiomers of 39–41 are even more potent than after 2 h.

We have previously reported that *trans*-1-piperazino-3-phenylindans also are inhibitors of DA and NE uptake but that this effect is confined to the (1*S*,3*R*)-enantiomers.^{1,33,34,38} This also proved to be true in the present series when some of the diastomers (with respect to 5-HT₂ affinity) were examined for amine uptake inhibiting properties (results not shown, but IC₅₀ values for inhibition of DA and NE uptake were in the range of 15–100 nM). For (+)-20 the IC₅₀ values were 70 and 50 nM for DA and NE uptake inhibition, respectively. The corresponding values for (-)-20 were 1900 and 2900 nM, respectively.

The eudismic ratio with regard to 5-HT₂ affinity varies for the enantiomeric pairs from 21 to 92. If one calculates a theoretical 5-HT₂ affinity of the diastomers based on the maximum content of the eutomer (Table III) one finds in all cases a lower affinity than what was actually found. However, for all diastomers except (+)-10 and (+)-39 the theoretical value is still within the 95% confidence ratio (2.05 for 5-HT₂ binding, see footnote Table IV). Therefore, for these compounds it cannot be completely excluded that the observed affinity of the diastomer is due to content of eutomer. The highest eudismic ratio was found for the enantiomeric pair of 41 (ratio: 92). However, (-)-41 was less selective with regard to D₂ and α₁ receptors than (-)-

20. This compound had overall the "best" profile, fulfilling the goals mentioned in the introduction, i.e., potent central effect (quipazine antagonism), high selectivity versus D₂ and α_1 receptors (ratios 182 and 191, respectively), and a high stereoselectivity (eudismic ratio: 68). This stereoselectivity is still considerably higher than that of the reference compounds mentioned in the introduction.

For the reasons mentioned above we assume that the active enantiomers in this series have the 1*R*,3*S* configuration. Previously we have shown that compounds with 1*S*,3*R* configuration are incompatible with a D₂ receptor interaction model proposed recently.^{38,22} Due to the fact that several of the compounds that so far have been shown to be compatible with the D₂ receptor interaction model are also potent and stereoselective 5-HT₂ antagonists, we used the "D₂ conformation" of 1 in our superimposition study with ketanserin.¹ The present work does not add any data that invalidate this proposed 5-HT₂ receptor active conformation of *trans*-1-piperazino-3-phenylindans. However, this study does add important data concerning the differences and similarities of aromatic substitution effects at the two sites (or rather three sites, because the study also contains information regarding α_1 adrenoceptor sites). We already knew that a 6-substituent in the indan benzene ring was required for high D₂ affinity^{1,35} and that substituents in the 4- and 5-positions were detrimental for D₂ affinity.³⁵ 7-Substituted derivatives retained some D₂ affinity³⁵ which was confirmed in the present study (compound 12). We also knew that unsubstituted or 6-substituted compounds had high 5-HT₂ affinity, but the present study shows that also 4-, 5-, and 7-substituted compounds have high 5-HT₂ affinity. The fact that 5-substitution also is destructive for α_1 adrenoceptor affinity was the key to developing selective 5-HT₂ antagonists. Finally, we have shown largely parallel substitution effects in relation to D₂ and 5-HT₂ affinity in the 3-phenyl ring, i.e., that high affinity is limited to 2- or 4-fluoro-substituted derivatives. The results obtained so far concerning the effect of aromatic substitution on 5-HT₂, D₂, and α_1 receptor affinity are summarized in Figure 2.

Recently, a number of selective D₂ antagonists of the benzamide type have been accommodated into the D₂ receptor-interaction model.³⁹ It is noteworthy that these compounds all are accommodated into the model using a concept where their benzene rings are superimposed on the phenyl ring in octoclothepein that corresponds to the 3-phenyl ring in the indans. It is therefore likely that the space occupied by the indan benzene ring corresponds to an essential binding pocket on the 5-HT₂ receptor and that this pocket has a size that apparently allows substitution in all four aromatic positions. The D₂ receptor must have a similar pocket, but apparently it is not essential that it is occupied by a benzene ring. However, if it is occupied by a benzene ring, it seems to be of crucial importance that this ring has a substituent which only is allowed in certain directions (Figure 2).³⁵ At the moment we are trying to use this information in the construction of three-dimensional models of the G-protein-coupled D₂ and 5-HT₂ receptor proteins. Further work is also in progress in order to refine the 5-HT₂ receptor model by conformational analyses and superimposition studies of a variety of 5-HT₂ antagonists.

Since we have not measured 5-HT_{1C} affinities we have not in this study been able to address the important question regarding 5-HT₂ versus 5-HT_{1C} affinity touched

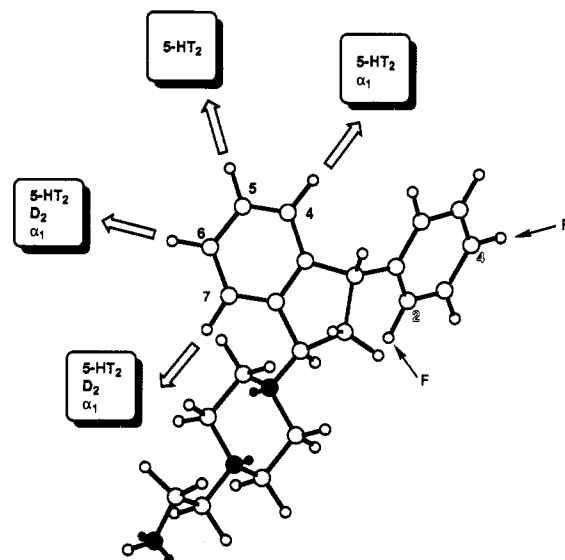


Figure 2. Summary of substitution effects in 1-piperazino-3-phenylindans (shown here with a *N*-(2-hydroxyethyl) substituent) extracted from the present paper and refs 1, 34, and 35. The compound is shown in the proposed D₂/5-HT₂ active conformation.^{1,22,38} The consequences of substitution in the four indan benzene ring positions on affinity for 5-HT₂, D₂, and α_1 receptors are shown. In the 3-phenyl ring high affinity is associated with a fluoro atom in either the 4- or the 2-position.

upon in the introduction. However, on the basis of the pharmacology presented here, it is unlikely that any of the compounds would have selectivity for 5-HT_{1C} receptors.

Finally, it should be mentioned that we have recently shown that the principle of obtaining 5-HT₂ selectivity (versus D₂ and α_1 affinity) by introducing substitutions in the indan ring 5-position also applies by substitution in the corresponding position in the related 1-phenyl- and 3-phenyl-substituted indoles (except in certain fluoro-substituted compounds).^{40,41}

Experimental Section

Melting points were determined on a Büchi SMP-20 apparatus and are uncorrected. ¹H NMR spectra were recorded of all novel compounds at 80 MHz on a Bruker WP 80 DS spectrometer or at 250 MHz on a Bruker AC 250 spectrometer. Deuterated chloroform (99.8% D) or dimethyl sulfoxide (99.9% D) was used as solvent. TMS was used as internal reference standard. Chemical shift values are expressed in ppm values. The following abbreviations are used for multiplicity of NMR signals: s = singlet, d = doublet, t = triplet, q = quintet, h = heptet, dd = double doublet, ddd = double doublet of doublets, dt = double triplet, m = multiplet. (*R*)-(-)-2,2,2-Trifluoro-1-(9-anthryl)-ethanol was purchased from Aldrich and used without purification. Spectra for determination of optical purity were recorded in chloroform-*d* on mixtures of the bases of the enantiomers and 2 equiv of the shift reagent.

The isomeric purity of all *trans* isomers (with respect to *cis* content) was determined by TLC with Merck silica gel 60 F₂₅₄ precoated plates and acetone-toluene-NH₄OH-2-propanol (60:40:2:2) as the developing solvent. The substances were visualized by spraying the completely dried plate with a mixture of concentrated sulfuric acid-37% formaldehyde solution (47:3), heating the plate for 5 min at 110 °C, and then observing it under an ultraviolet source at 365 nm. In order to obtain satisfactory sensitivity, sometimes it was necessary to spray with 5% potassium dichromate in 40% sulfuric acid and to heat at 110 °C for 20 min. The estimation of isomeric purity was based on comparison with small samples of the *cis* isomer or small samples of the *trans* isomer itself. *Trans* isomers had in all cases the lowest *R_f* values. Content of water in crystalline compounds was

determined by Karl Fischer titration. Microanalyses were performed by Lundbeck Analytical Department, and results obtained were within $\pm 0.4\%$ of the theoretical values.

Preparation of Heterocyclic Chloroalkyl Side Chains. The side chains were prepared as previously described.¹ 1-(2-Chloroethyl)-3-phenyl-2-imidazolidinone and 6-(2-chloroethyl)-7-methyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one were prepared by published methods.^{42,43}

Method A. The procedure was as previously published for preparation of 9, 11, and 13.^{34,35}

Optical Resolution of *trans*-4-[5-Fluoro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]-1-piperazineethanol (13). The dihydrochloride salt of 13³⁴ (11 g, 0.026 mol) was converted to the base (9.5 g). A solution of the base and L-(+)-tartaric acid (4 g, 0.027 mol) in ethanol (250 mL) was kept at room temperature for 18 h. The crystals were filtered off, dried (4.5 g), and recrystallized from methanol (600 mL) to give 3.2 g of 13. L-(+)-Tartrate: mp 216–217 °C; $[\alpha]^{22}_D +15.4^\circ$ (c 0.5, DMSO). The L-(+)-tartrate salt was converted to the base and transformed to the dihydrochloride salt which was recrystallized from ethanol-ether to give 1 g (19%) of (+)-13-dihydrochloride: mp 224–226 °C; $[\alpha]^{22}_D +27.1^\circ$ (c 0.5, CH₃OH); ¹H NMR (base in CDCl₃) δ 2.04 (dt, 1H), 2.42–2.64 (m, 10H), 2.71 (ddd, 1H), 3.61 (t, 2H), 4.34 (dd, 1H), 4.40 (t, 1H, H₃), 6.62 (dd, 1H), 6.88–7.12 (m, 5H), 7.34 (dd, 1H). Anal. (C₂₁H₂₆Cl₂F₂N₂O) C, H, N.

The first filtrate from the L-(+)-tartrate salt was evaporated and converted to the base. The base was treated with D-(–)-tartaric acid. The resulting D-(–)-tartrate was recrystallized and converted to the dihydrochloride salt as described for (+)-13. There was obtained 0.6 g (11%) of (–)-13-dihydrochloride: mp 223–226 °C; $[\alpha]^{22}_D -27.1^\circ$ (c 0.5, CH₃OH); ¹H NMR (base in CDCl₃) identical to (+)-13. Anal. (C₂₁H₂₆Cl₂F₂N₂O) C, H, N.

***trans*-4-[5-Chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]-1-piperazineethanol (10)** was resolved in a similar way to give (+)-10-dihydrochloride [mp 224–227 °C; $[\alpha]^{22}_D +13.5^\circ$ (c 0.5, H₂O)] and (–)-10-dihydrochloride: mp 224–227 °C; $[\alpha]^{22}_D -14.1^\circ$ (c 0.5, H₂O); ¹H NMR (base in CDCl₃) δ 2.03 (dt, 1H), 2.40–2.62 (m, 10H), 2.70 (ddd, 1H), 3.60 (t, 2H), 4.35 (dd, 1H), 4.40 (t, 1H, H₃), 6.92 (s, 1H), 6.93–7.10 (m, 4H), 7.22 (dd, 1H), 7.33 (dt, 1H). Anal. (C₂₁H₂₆Cl₃FN₂O) C, H, N.

Method B. *trans*-1-[2-[4-[5-Chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]-3-isopropyl-2-imidazolidinone Dimaleate (20). A mixture of 43 (140 g, 0.31 mol, as the maleate salt, see below), 1-(2-chloroethyl)-3-isopropyl-2-imidazolidinone (75 g, 0.39 mol), potassium carbonate (260 g, 1.88 mol), and potassium iodide (5 g) in methyl isobutyl ketone (1 L) was refluxed with stirring for 18 h. After the mixture was cooled, water (500 mL) was added. The phases were separated, and the organic layer was washed with water and then concentrated in vacuo. The residue was dissolved in ether, washed with water, and extracted with 1 N methanesulfonic acid. The base was liberated with 9 N NaOH, extracted with ether, dried, and concentrated in vacuo to give 157 g of crude 20. The base was converted to the dimaleate salt in ethanol (2 L) to give 193 g (87%) of 20-dimaleate. A sample recrystallized from methanol melted at 188–190 °C; isomeric purity >99% *trans* isomer (TLC). ¹H NMR: see (–)-20. Anal. (C₃₅H₄₂ClFN₄O₉) C, H, N.

Optical Resolution of 20. The resolution was performed essentially as described above for 13 (using L-(+)- and D-(–)-tartaric acid) with the exception that tartrate salts were crystallized and recrystallized from water. From 126 g (0.26 mol) of 20 (as the base) there was obtained 51 g of 20-L-(+)-tartrate salt: mp 102–104 °C, and 50 g of 20-D-(–)-tartrate salt: mp 102–104 °C. In a conventional manner the tartrate salts were converted to the maleate salts which were recrystallized from ethanol to give 40 g (43%) of (+)-20-dimaleate [mp 174.9–175.3 °C; $[\alpha]^{22}_D +17.0^\circ$ (c 0.5, CH₃OH)] and 40 g (43%) of (–)-20-dimaleate: mp 175.0–175.3 °C; $[\alpha]^{22}_D -17.5^\circ$ (c 0.5, CH₃OH), respectively. ¹H NMR (base in CDCl₃) δ 1.11 (d, 6H), 2.02 (dt, 1H), 2.43–2.63 (m, 10H), 2.70 (ddd, 1H), 3.18–3.38 (m, 6H), 4.13 (h, 1H), 4.34 (dd, 1H), 4.39 (t, 1H, H₃), 6.91 (s, 1H), 6.93–7.10 (m, 4H), 7.21 (dd, 1H), 7.33 (d, 1H). Anal. (C₃₅H₄₂ClFN₄O₉) C, H, N.

Preparation and Resolution of *trans*-1-[5-Chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazine Maleate (43). Thionyl chloride (44 mL, 0.6 mol) was added dropwise with water cooling to a solution of 5-chloro-3-(4-fluorophenyl)-

2,3-dihydro-1*H*-inden-1-ol (131 g, 0.5 mol) in ether (2 L) containing a catalytic amount of DMF (0.5 mL). The mixture was stirred for 2 h at room temperature, poured into ice, and neutralized with 9 N NaOH. The organic phase was separated, dried (MgSO₄), and evaporated to give 140 g (100%) of crude 1,5-dichloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-indene. A mixture of the chloro derivative (140 g, 0.5 mol), piperazine (800 g, 9.3 mol), and acetone (2 L) was refluxed with stirring for 18 h. After the mixture was cooled, piperazine hydrochloride was filtered off and washed with ethyl acetate. The combined filtrate was concentrated in vacuo. The residue was dissolved in ether, washed with water, and extracted with 1 N methanesulfonic acid. The base was liberated from the acid extract with 9 N sodium hydroxide, extracted with ether, dried (MgSO₄), and evaporated in vacuo to give crude 43 (156 g, 94%). The residue (0.47 mol) was dissolved in acetone (600 mL) and ethanol (600 mL), whereupon maleic acid (110 g, 0.95 mol) was added. After 1 h at room temperature the monomaleate salt of 43 was filtered and dried: yield 216 g (96.6%); mp 190–191 °C.

A total of 10 g was recrystallized from ethanol to give analytically pure 43-maleate: mp 194–195 °C; ¹H NMR (DMSO-*d*₆) δ 2.11 (dt, 1H), 2.45–2.67 (m, 3H), 2.67–2.83 (m, 2H), 3.00–3.17 (m, 4H), 4.42–4.56 (m, 2H), 6.04 (s, 2H), 6.94 (s, 1H), 7.07–7.25 (m, 4H), 7.33 (dd, 1H), 7.40 (d, 1H), 8.52 (br s, 1H). Anal. (C₂₃H₂₄ClFN₂O₄), C, H, N. A solution of 43 (24 g, 0.073 mol) and (–)-dibenzoyl-L-tartaric acid hydrate ((–)-DBT) (27.3 g, 0.073 mol) in acetone (250 mL) was left for 18 h at room temperature. The crystals were filtered and dried. The (–)-DBT salt was boiled with methanol (1 L), cooled, filtered, and dried to give 13.5 g of 43 (–)-DBT salt, mp 213–214 °C. The first filtrate from the (–)-DBT salt was concentrated and converted to the base (13 g), which was treated with (+)-DBT in the same manner as described for the (–)-DBT salt to yield 11 g of 43 (+)-DBT salt, mp 212–213 °C.

The DBT salts were converted to the bases and then precipitated as maleate salts to afford (+)-43-maleate (mp 189–190 °C) and (–)-43-maleate, mp 187–188 °C. The maleate salts were recrystallized from a mixture of ethanol (200 mL) and methanol (50 mL) to give 1.2 g (7.4%) of (+)-43-maleate salt: mp 194–196 °C; $[\alpha]^{22}_D +30.6^\circ$ (c 0.5, CH₃OH) and 1.3 g (8.0%) of (–)-43-maleate salt: mp 194–196 °C; $[\alpha]^{22}_D -30.2^\circ$ (c 0.5, CH₃OH). Anal. (C₂₃H₂₄ClFN₂O₄), C, H, N.

Method C. (+)-*trans*-1-[2-[4-[5-Chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]tetrahydro-2(1*H*)-pyrimidinethione Dihydrochloride ((+)-39). To a solution of (+)-43 (59 g of base, 0.17 mol; from 73 g of maleate salt, mp 193–195 °C) in methanol (500 mL) was added in one portion a 20% solution of ethylene oxide (9.2 g (10.4 mL), 0.21 mol) in methanol. The mixture was stirred overnight. No starting material could be detected on TLC, and the reaction mixture was evaporated in vacuo. The residue was dissolved in 1 N methanesulfonic acid and washed with ether. The base was liberated with 10 N NaOH, extracted with dichloromethane, dried, and evaporated in vacuo to give 62 g of crude (+)-10.

The crude (+)-10 was dissolved in trichloromethane (100 mL) was added to a refluxing solution of thionyl chloride (100 mL) and DMF (1 mL) in trichloromethane (2 L) during 5 min. The mixture was refluxed for 1 h and cooled, and the precipitated hydrochloride was filtered, washed with ethyl acetate, and dried to give 52 g of crude *trans*-1-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]-4-(2-chloroethyl)piperazine-dihydrochloride, mp 272–275 °C.

A mixture of this hydrochloride salt and 1,3-diaminopropane (100 mL) in ethanol (500 mL) was refluxed with stirring for 1.5 h. The mixture was concentrated in vacuo; the residue was dissolved in a mixture of dichloromethane and water, and the organic layer was separated, washed with saturated NaCl solution, dried (MgSO₄), and evaporated in vacuo to give 69 g of the crude enantiomer of *trans*-1-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]-4-[2-[(3-amino-1-propyl)amino]ethyl]piperazine as an oil.

The propylenediamine derivative (25 g) was dissolved in *n*-pentanol, and carbon disulfide (15 mL) was added. The mixture was kept for 1 h at room temperature, whereupon excess carbon disulfide was removed in vacuo. The dithiocarbamate salt in *n*-pentanol was refluxed for 1 h (evolution of hydrogen sulfide).

The reaction mixture was concentrated in vacuo. The residue was dissolved in ether and extracted with 1 N methanesulfonic acid. The base was liberated with 9 N NaOH and extracted with dichloromethane. The dried and concentrated dichloromethane solution gave an oil containing the target compound and starting material, which were separated by column chromatography on silica gel (eluted with acetone-toluene-2-propanol-NH₄OH (60:40:2:2)). This afforded 9 g of the title compound as the base which was converted to the dihydrochloride salt. After recrystallization from methanol (600 mL) there was obtained 6 g (6.5% from (+)-38) of (+)-39-dihydrochloride: mp 212–213 °C; [α]_D²² +6.6° (c 0.5, water). Anal. (C₂₅H₃₂Cl₃FN₄S) C, H, N. From (-)-43 there was in a similar way obtained 5.6 g of (-)-*trans*-1-[2-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]tetrahydro-2(1*H*)-pyrimidinone-dihydrochloride, (-)-39: mp 212–213 °C; [α]_D²² -6.6° (c 0.5, water); ¹H NMR (base in CDCl₃) δ 1.93–2.10 (m, 3H), 2.40–2.77 (m, 9H), 2.67 (t, 2H), 3.22–3.33 (m, 2H), 3.41 (t, 2H), 3.97 (t, 2H), 4.36 (dd, 1H), 4.39 (t, 1H, H₃), 6.41 (br s, 1H), 6.91 (s, 1H), 6.93–7.08 (m, 4H), 7.21 (dd, 1H), 7.33 (d, 1H). Anal. (C₂₅H₃₂Cl₃FN₄S) C, H, N.

(+)-*trans*-1-[2-[4-[5-Chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]tetrahydro-2(1*H*)-pyrimidinone Dimaleate, ((+)-41). This compound was prepared as described for (+)-39 above, except that carbon disulfide was replaced with urea in the last step: A mixture of the propylenediamine derivative obtained from (+)-43 (40 g) and urea (5 g) in 1-methyl-2-pyrrolidinone (100 mL) was heated at 140 °C for 1 h and at 170 °C for 3 h. The reaction mixture was poured on ice and extracted with ethyl acetate. The organic phase was washed with brine, dried, and concentrated in vacuo. The resulting oil was purified by column chromatography using ethyl acetate-methanol-triethylamine (80:10:10) as eluent, yielding 11 g of the base of (+)-41. The dimaleate salt was crystallized from ethanol-acetone and was recrystallized from methanol-ether to give 5.6 g (8.2%) of (+)-41-dimaleate: mp 179–180 °C; [α]_D²² +16.8° (c 0.5, water); ¹H NMR (base in CDCl₃) δ 1.85–1.97 (m, 2H), 2.02 (dt, 1H), 2.41–2.63 (m, 10H), 2.70 (ddd, 1H), 3.23–3.37 (m, 4H), 3.41 (t, 2H), 4.34 (dd, 1H), 4.39 (t, 1H, H₃), 4.76 (br s, 1H), 6.91 (s, 1H), 6.92–7.10 (m, 4H), 7.21 (dd, 1H), 7.33 (d, 1H). Anal. (C₃₃H₃₈ClFN₄O₉) C, H, N.

In a similar way there was obtained 2.1 g of (-)-*trans*-1-[2-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]tetrahydro-2(1*H*)-pyrimidinone-dimaleate, (-)-41: mp 179–180 °C; [α]_D²² -17.2° (c 0.5, water). Anal. (C₃₃H₃₈ClFN₄O₉) C, H, N.

The corresponding 5-fluoro derivatives of (+)/(-)-39 and (+)/(-)-41 was obtained in a similar way starting with the pure enantiomers (+)- and (-)-13. The physicochemical properties of the fluoro derivatives were as follows:

(+)-*trans*-1-[2-[4-[5-Fluoro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]tetrahydro-2(1*H*)-pyrimidinone-dihydrochloride, (+)-40: mp 205–206 °C; [α]_D²² +26.7° (c 0.5, water); ¹H NMR (base in CDCl₃) δ 1.90–2.10 (m, 3H), 2.40–2.75 (m, 9H), 2.64 (t, 2H), 3.24 (t, 2H), 3.39 (t, 2H), 3.94 (t, 2H), 4.32 (dd, 1H), 4.38 (t, 1H, H₃), 6.58 (d, 1H), 6.67 (br s, 1H), 6.84–7.10 (m, 5H), 7.34 (dd, 1H). Anal. (C₂₅H₃₂Cl₂F₂N₄S) C, H, N.

(-)-*trans*-1-[2-[4-[5-Fluoro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]tetrahydro-2(1*H*)-pyrimidinone-dihydrochloride, (-)-40: mp 205–206 °C; [α]_D²² -25.6° (c 0.5, water). Anal. (C₂₅H₃₂Cl₂F₂N₄S) C, H, N.

(+)-*trans*-1-[2-[4-[5-Fluoro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]tetrahydro-2(1*H*)-pyrimidinone-dimaleate, (+)-42: mp 170–171 °C; [α]_D²² +16.0° (c 0.5, water); ¹H NMR (base in CDCl₃) δ 1.86–2.00 (qui, 2H), 2.03 (dt, 1H), 2.40–2.63 (m, 10H), 2.71 (ddd, 1H), 3.21–3.33 (m, 4H), 3.44 (t, 2H), 4.33 (dd, 1H), 4.40 (t, 1H, H₃), 5.06 (br s, 1H), 6.60 (dd, 1H), 6.88–7.10 (m, 5H), 7.34 (dd, 1H). Anal. (C₃₃H₃₈F₂N₄O₉) C, H, N.

(-)-*trans*-1-[2-[4-[5-Fluoro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]tetrahydro-2(1*H*)-pyrimidinone-dimaleate, (-)-42: mp 170–171 °C; [α]_D²² -15.0° (c 0.5, water). Anal. (C₃₃H₃₈F₂N₄O₉) C, H, N.

trans-1-[2-[4-[5-Chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]-3-(2-hydroxyethyl)-2-

imidazolidinone Dimaleate (19). Compound 16 (4.4 g as the base, 0.01 mol) was added to a suspension of potassium *tert*-butoxide (1.7 g, 0.015 mol) in dry toluene (200 mL). The mixture was kept at room temperature for 1 h with stirring, whereupon ethyl bromoacetate (2.5 g, 0.015 mol) was added. The mixture was stirred for 1 h at room temperature and was then poured into ice. The organic phase was separated, washed with water, dried, and evaporated in vacuo. The resulting oil was dissolved in dry tetrahydrofuran (150 mL), whereupon lithium borohydride (1 g) was added. The mixture was stirred for 1 h at room temperature and was then evaporated in vacuo. The residue was treated with ether and 1 N methanesulfonic acid. The acid phase was basified with 9 N sodium hydroxide and extracted with dichloromethane. After drying and evaporation in vacuo there was obtained 2.5 g of 19, which was converted to the dimaleate salt (in acetone). The salt was recrystallized from ethanol-methanol to give 1.4 g (19%) of pure 19: mp 168–170 °C; ¹H NMR (the base in CDCl₃) δ 2.01 (dt, 1H), 2.38–2.62 (m, 10H), 2.68 (ddd, 1H), 3.22–3.36 (m, 4H), 3.38 (s, 4H), 3.73 (s, 2H), 4.33 (dd, 1H), 4.38 (t, 1H, H₃), 6.89 (s, 1H), 6.91–7.10 (m, 4H), 7.19 (dd, 1H), 7.33 (d, 1H). Anal. (C₃₄H₄₀ClFN₄O₁₀) C, H, N.

Pharmacological Test Methods. Animals. Male Wistar rats (Mol:Wist, SPF, 170–270 g) were used. We have recently described the handling procedures in detail.⁴⁴

Calculations. ED₅₀ values were calculated by log-probit analyses. IC₅₀ values were estimated from concentration-effect curves using a log-concentration scale. Details are available from the references cited in the description of specific test methods below.

Antagonism of Quipazine-Induced Head Twitches. The experimental details are given by Arnt et al.² Test compounds were injected sc or po to rats 2 or 24 h before quipazine (15 μ mol/kg, sc). Head twitches were counted 30–40 min after the quipazine treatment. The number of head twitches in the drug-treated group (at least four animals per dose) was expressed as a percentage of the number of head twitches in a quipazine-treated control group.

Antagonism of Pergolide-Induced Circling Behavior in Rats with Unilateral 6-OHDA Lesions. This test method is described in detail by Arnt and Hyttel.⁴⁵ Contralateral circling is induced in 6-OHDA-lesioned rats in response to administration of pergolide (0.05 μ mol/kg, sc). Test compounds were injected sc 2 h before pergolide. The effect of individual doses of test drugs was calculated as a percentage of the mean effect of control sessions 1 week before and 1 week after the test session for each rat (at least four rats per dose).

Receptor Binding. DA D₂ Receptors. Affinity of test compounds to dopamine D₂ receptors was estimated by their ability to displace ³H-spiperone from rat striatal membranes as described by Hyttel.⁴⁶

5-HT₂ Receptors. Affinity of test compounds to serotonin 5-HT₂ receptors was estimated by their ability to displace ³H-ketanserin from rat cortical membranes as described by Hyttel.⁴⁶

α_1 Adrenoceptors. Affinity of test compounds to α_1 adrenoceptors was estimated by their ability to displace ³H-prazosin from whole rat brain membranes as described by Skarsfeldt and Hyttel.⁴⁷

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