Stereospecific and Selective 5-HT_2 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-HT_2, D_2, and α_1 receptor affinity in a subseries of new and previously synthesized 1-piperazino-3-phenylindans indicated that high 5-HT_2 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-HT_2 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 analogoues. 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 D_2 and α_1 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 D_2 receptor interaction model. While there are no indications so far that *trans*-1-piperazino-3-phenylindans interact with D_2 and 5-HT_2 receptors in different conformations, the present study shows important differences in aromatic substitution effects. Only 5-HT_2 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 serotonin$_2$ (5-HT_2) 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-HT_2 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) D_2 receptors and α_1 adrenoceptors.[1]

Centrally acting 5-HT_2 antagonists have shown promising effects in animal models for anxiety[3] and depression[4] as well as in certain drug-abuse models.[5–7] Clinical investigations with the 5-HT_2 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 symptoms[11] and extrapyramidal symptoms[12–14] have been demonstrated. A prophylactic effect of 5-HT_2 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-HT_2 and 5-HT_{1C} receptors, and they share the same second messenger system (phosphoinositide hydrolysis).[16,17] Phylogenetic 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-HT_2 receptors also have high affinity for 5-HT_{1C} receptors (e.g., ritanserin has high affinity for both subtypes).[19] While 5-HT_2 antagonists such as ketanserin and MDL 11939[20] (**4**, Figure 1) show moderate to high selectivity for 5-HT_2 receptors versus 5-HT_{1C} receptors, no selective 5-HT_{1C} antagonist has yet been described.[19]

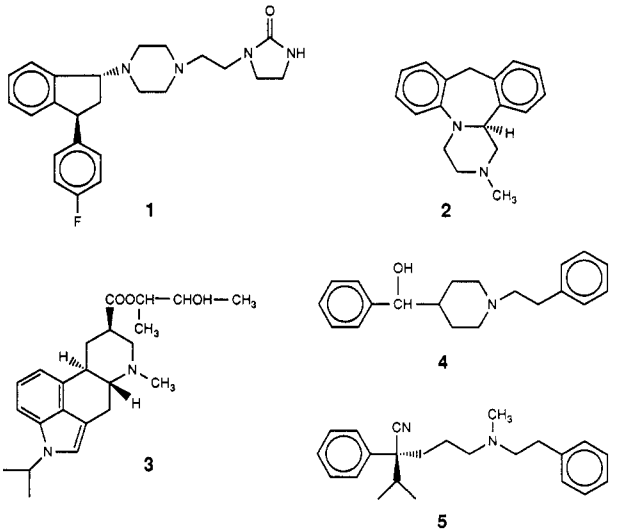

Figure 1. Structures of chiral 5-HT_2 antagonists.

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

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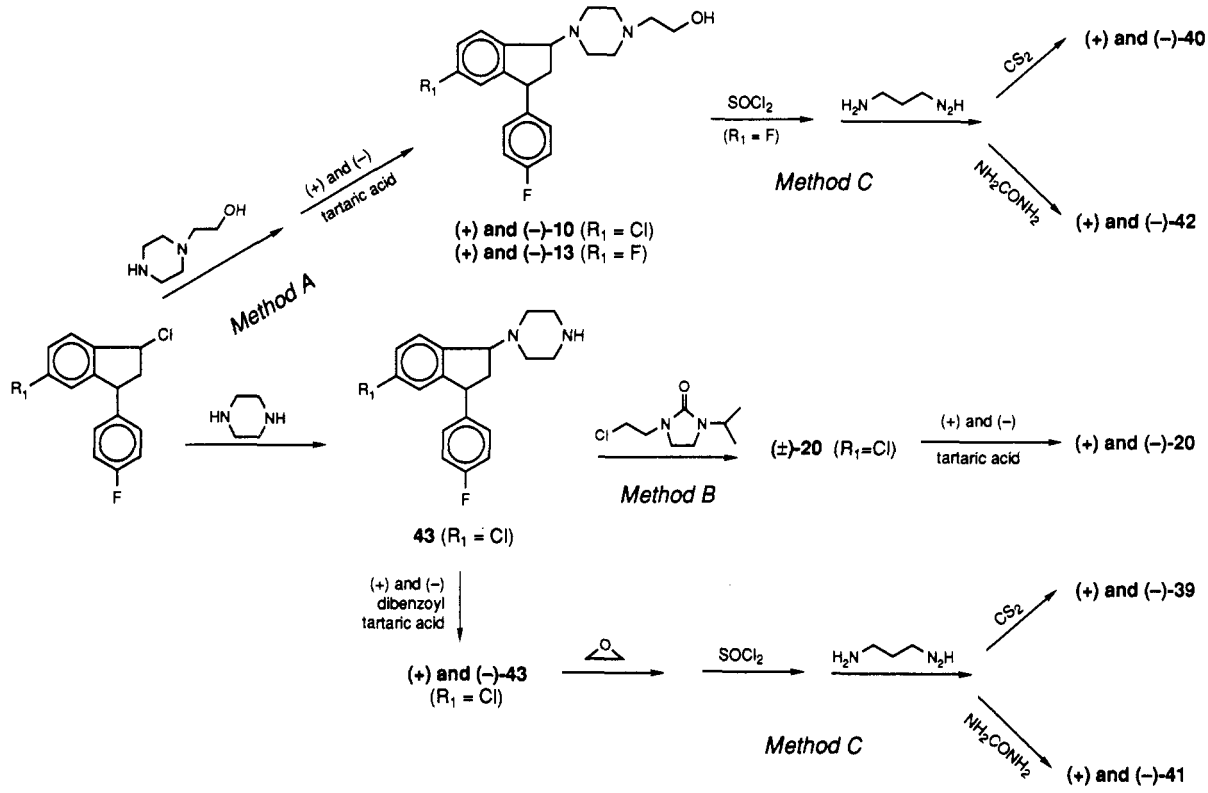
Scheme I



lective 5-HT_2 antagonists, such as methiothepine[21] or octoclothepine,[22] have equal, high affinity for the 5-HT_2 receptor. The (*S*)-(+)-enantiomer of the antidepressant mianserin (**2**) has only 4–5 times higher affinity for serotonin receptors than its corresponding (*R*)-enantiomer (^{3}H-mianserin binding).[23,24]

1-Isopropyl-substituted ergolines, such as LY53857[25] (**3**), its corresponding 8-(4-methoxycyclohexyl) ester, sergolexole,[26] and the *N*-cyclohexyl-8-carboxamide analogue, LY237733,[27] are all potent and selective 5-HT_2 antagonists with respect to D_2 receptors and α_1 adrenoceptors. However, LY237733 has similar affinity for 5-HT_2 and 5-HT_{1C} receptors.[27] While it has been reported that the four side chain stereoisomers of **3** have similar 5-HT_2 receptor affinity,[28] there is no information in the literature concerning 5-HT_2 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 ratio[29] of 9).[31] The mixed calcium antagonist/5-HT_2 antagonist (*S*)-emopamil (**5**) has a 13 times higher affinity for the 5-HT_2 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-HT_2 versus D_2 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-HT_2 receptors.[33] However, like other 6-substituted *trans*-1-piperazino-3-phenylindans[34] the active enantiomer had also high affinity for D_2 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-HT_2 antagonistic activity, (2) high selectivity versus D_2 receptors and α_1 adrenoceptors, and (3) high stereoselectivity toward 5-HT_2 receptors. In this paper we report 5-HT_2 affinity and 5-HT_2 antagonism in vivo of a new series of 5-substituted compounds as well as of certain compounds which we previously have examined for D_2 antagonistic effects.[34,35]

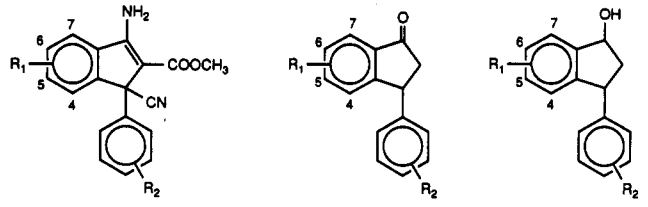
Chemistry

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]

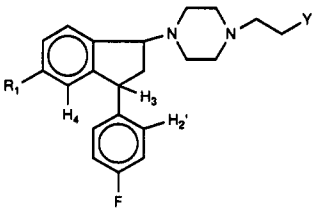
compd[b]	mp, °C	recrystn solv[c]	yield (%)	formula[d]
6h	215–217	IPE	48	$C_{19}H_{15}FN_2O_2$
6j	192–194	T	46	$C_{18}H_{13}ClN_2O_2$
6k	227–228	D/EA	31	$C_{18}H_{12}ClFN_2O_2$
6l	192–193	IPE	52	$C_{18}H_{12}ClFN_2O_2$
6m	213–215	T	35	$C_{18}H_{12}Cl_2N_2O_2$
6n	228–230	DMF/H_2O	63	$C_{19}H_{15}ClN_2O_2$
7a	74–76	C	61	$C_{15}H_{10}ClFO$
7b	84–86	IPE/H	92	$C_{15}H_{10}ClFO$
7d	113–116	not recryst	79	$C_{15}H_{10}ClFO$
7f	105–106	IPE	81	$C_{16}H_{10}F_4O$
7g	117–119	IPE	77	$C_{15}H_{10}BrFO$
7h	69–71	IPE	63	$C_{16}H_{13}FO$
7i[e]	74–76	IPE	43	$C_{16}H_{13}FOS$
7j	127–129	IPE	64	$C_{15}H_{11}ClO$
7k	83–85	P	46	$C_{15}H_{10}ClFO$
7l	118–119	IPE	64	$C_{15}H_{10}ClFO$
7m	140–142	H	77	$C_{15}H_{10}Cl_2O$
7n	112–114	H	82	$C_{16}H_{13}ClO$
8a	107–109	C	65	$C_{15}H_{12}ClFO$
8b	92–93	C	44	$C_{15}H_{12}ClFO$
8d	102–104	C	79	$C_{15}H_{12}ClFO$
8f	81–83	P	97	$C_{16}H_{12}F_4O$
8g	107–109	IPE/P	82	$C_{15}H_{12}BrFO$
8h	100–102	IPE/P	89	$C_{16}H_{15}FO$
8i	114–116	IPE/EA	83	$C_{16}H_{15}FOS$
8j	110–111	IPE	83	$C_{15}H_{13}ClO$
8k	78–80	IPE/P	85	$C_{15}H_{12}ClFO$
8l	110–112	P	84	$C_{15}H_{12}ClFO$
8m	129–131	H	85	$C_{15}H_{12}Cl_2O$
8n	oil			$C_{16}H_{15}ClO$

[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′-CH_3S-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 I. 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 scale up the resolution of the corresponding nor-derivative **43** (Scheme I). 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**.

Table III. Optical Purity and ^{1}H NMR Chemical Shifts of H_3 of Resolved Compounds



compd	δ H_3[a] (ppm)	$\Delta\delta$ 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

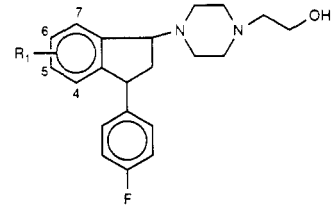
[a] Chemical shift value without (*R*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol. [b] Upfield chemical shift displacement induced by addition of 2 equiv of (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol.

The optical purity of the resolved compounds was determined by ^{1}H 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 octoclothepin enantiomers.[22] The chemical shift of H_3 (assigned by long-range coupling to H_4 in the indan ring system and the $H_{2'}$, 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 H_3 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 H_3 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 1*R*,3*S*.[1] Comparison of the CD-spectra of **1** with other resolved D_2 and/or 5-HT_2 antagonists from the *trans*-1-piperazino-3-phenylindan class of compounds have invariably shown that the more potent enantiomer has the 1*R*,3*S* configuration.[1,33] Therefore, we assume that the configuration of the eutomers of the resolved compounds in this series also have the 1*R*,3*S* configuration.

The sign of the optical rotation is *not* generally indicative of the absolute configuration. Within D_2/5-HT_2-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-phenylidans[a]



compd[b]	R_1	mp (°C)	formula[c]	receptor binding[d] 5-HT_2	D_2	α_1	quipazine inhibition (rats)[e]
9	4-Cl	*f*	*f*	40	220	30	0.82 (0.18–3.7)
10	5-Cl	267–270	$C_{21}H_{24}ClFN_2O\cdot 2HCl$	25	2200	230	0.23 (0.066–0.81)
(+)-**10**	5-Cl	224–227	$C_{21}H_{24}ClFN_2O\cdot 2HCl$	230	6300	2500	>2.8
(−)-**10**	5-Cl	224–227	$C_{21}H_{24}ClFN_2O\cdot 2HCl$	11	370	210	0.86 (0.45–1.7)
11	6-Cl	*g*	*g*	2.6	20	26	0.039 (0.014–0.11)
12	7-Cl	140–142	$C_{21}H_{24}ClFN_2O\cdot$dimaleate	15	46	38	1.3 (0.30–5.7)
13	5-F	*g*	*g*	21	1100	150	0.35 (0.08–1.5)
(+)-**13**	5-F	224–226	$C_{21}H_{24}F_2N_2O\cdot 2HCl$	12	330	72	0.33 (0.11–1.0)
(−)-**13**	5-F	223–226	$C_{21}H_{24}F_2N_2O\cdot 2HCl$	500	22000	1100	>2.8
14	5-CF_3	172–174	$C_{22}H_{24}F_4N_2O\cdot$dimaleate	8.9	1300	380	1.0 (0.27–3.7)
15	5-CH_3	169–171	$C_{22}H_{27}FN_2O\cdot$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 IC_{50} 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 IC_{50} 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: D_2, 2.25; α_1, 2.20; 5-HT_2, 2.05. [e] Results are expressed as ED_{50} 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.

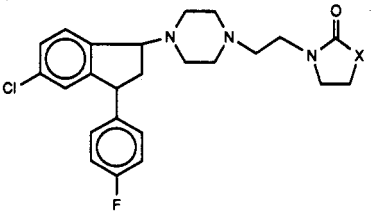
Results and Discussion

Details concerning the test methods are described in the Experimental Section. Affinities for brain 5-HT_2 receptors, D_2 receptors and α_1 adrenoceptors of all compounds are shown in Tables IV–VII. Antagonism of the characteristic head-twitch syndrome, induced by the 5-HT_2 agonist quipazine, was used as a measure of central 5-HT_2 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.

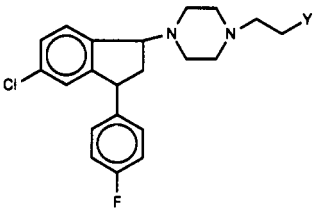
In Table IV is shown a series of *N*-(2-hydroxyethyl)-substituted compounds. We have previously shown that the 5-fluoro-substituted derivative **13** was very weak or inactive in neuroleptic test models reflecting in vivo D_2 antagonism.[34] More recently, the effect of aromatic substitution on D_2 affinity 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 D_2 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-HT_2 antagonist ketanserin.[1] Inspection of this preliminary 5-HT_2 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-HT_2 activity, and as can be seen from Table IV, these compounds indeed had significant 5-HT_2 affinity and 5-HT_2-antagonistic activity in vivo. Interestingly, these two compounds had very low α_1 affinity compared with 1 (Table VII) and its analogues.[1] A similar selective profile was found for the 5-CF_3- and the 5-CH_3-substituted derivatives **14** and **15**, but these compounds were less potent in vivo. Resolution of **10** and **13** revealed that the 5-HT_2-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-HT_2 activity, but the 4-chloro derivative was equally potent on α_1 adrenoceptors and the 7-chloro derivative had both significant D_2 and α_1 affinity. The 6-chloro derivative **11** is a potent neuroleptic compound,[34] but was still the most potent 5-HT_2 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 derivatives[1] indicated that 5-HT_2 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-HT_2 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

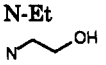
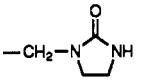
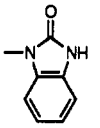
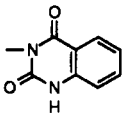
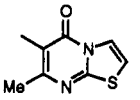
Table V. Effect of Side Chain Variations in a Series of 5-Chloro-4′-fluoro-Substituted *trans*-1-Piperazino-3-phenylindans[a]



Type I

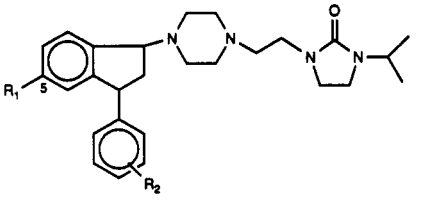


Type II

compd[b]	type	X/Y	mp (°C)	formula[c]	receptor binding[d] 5-HT$_2$	D_2	α_1	quipazine inhibition (rats)[e]
16	I	NH	168–170	$C_{24}H_{28}ClFN_4O$	2.9	360	200	0.34 (0.16–0.71)
17	I	N-Me	164–166	$C_{25}H_{30}ClFN_4O$·dimaleate	2.8	190	600	0.093 (0.052–0.17)
18	I	N-Et	178–180	$C_{26}H_{32}ClFN_4O$·dimaleate	2.6	260	240	0.042 (0.0088–0.20)
19	I		168–170	$C_{26}H_{32}ClFN_4O_2$·dimaleate	6.1	320	710	1.1 (0.41–3.0)
20	I	N-iPr	188–190	$C_{27}H_{34}ClFN_4O$·dimaleate	3.9	280	260	0.060 (0.024–0.15)
(+)-20	I	N-iPr	174.9–175.3	$C_{27}H_{34}ClFN_4O$·dimaleate	75	1300	340	>7.0
(−)-20	I	N-iPr	175.0–175.3	$C_{27}H_{34}ClFN_4O$·dimaleate	1.1	200	210	0.031 (0.0079–0.12)
21	I	N-Ph	174–176	$C_{30}H_{32}ClFN_4O$·dimaleate	44	300	310	>6.7
22	I	CH_2	250–252	$C_{25}H_{29}ClFN_3O$·2HCl	10	500	370	2.7 (1.4–5.1)
23[f]	I	O	244–246	$C_{24}H_{27}ClFN_3O_2$·2HCl	23	550	140	2.0 (0.57–7.0)
24	II		159–160	$C_{25}H_{30}ClFN_4O$·dimaleate	10	160	73	0.91 (0.08–10)
25	II		192–194	$C_{28}H_{28}ClFN_4O$·dimaleate	5.6	110	66	0.21 (0.11–0.41)
26	II		195–198	$C_{29}H_{28}ClFN_4O_2$·dimaleate	3.8	93	78	>3.3
27	II		202–203	$C_{28}H_{28}ClFN_4OS$·dimaleate	19	65	24	1.9 (0.36–9.9)

[a–e] See corresponding footnotes to Table IV. [f] 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]



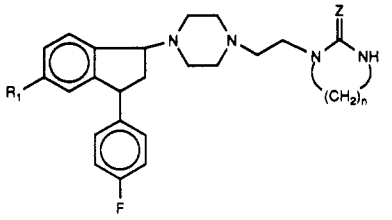
compd[b]	R_1	R_2	mp (°C)	formula[c]	receptor binding[d] 5-HT$_2$	D_2	α_1	quipazine inhibition (rats)[e]
28	Br	4-F	180–182	$C_{27}H_{34}BrFN_4O$·dimaleate	6.4	240	270	0.098 (0.022–0.43)
29	CF_3	4-F	174–176	$C_{28}H_{34}F_4N_4O$·dimaleate	3.7	510	370	0.13 (0.076–0.22)
30	CH_3	4-F	178–180	$C_{28}H_{37}FN_4O$·dimaleate	3.0	450	120	0.20 (0.12–0.32)
31	SCH_3	4-F	140	$C_{28}H_{37}FN_4OS$·H_2O	4.0	720	250	>3.4
32	Cl	H	189–191	$C_{27}H_{35}ClN_4O$·dimaleate	9.9	750	510	1.0 (0.26–3.9)
33	Cl	2-F	190–192	$C_{27}H_{34}ClFN_4O$·dimaleate	3.5	920	670	2.1 (0.55–8.0)
34	Cl	3-F	180–182	$C_{27}H_{34}ClFN_4O$·dimaleate	26	490	970	NT[f]
35	Cl	4-Cl	170–172	$C_{27}H_{34}Cl_2N_4O$·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–e] See corresponding footnotes to Table IV. [f] 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] 5-HT_2	D_2	α_1	quipazine inhibition (rats)[e]
37	Cl	S	1	183–184	$C_{24}H_{28}ClFN_4S$·dimaleate	1.5	67	52	0.077 (0.027–0.22)
38	F	S	1	172–174	$C_{24}H_{28}F_2N_4S$·dimaleate	1.5	230	110	0.12 (0.044–0.32)
39	Cl	S	2	184–185	$C_{25}H_{30}ClFN_4S$·dimaleate	1.5	93	170	0.048 (0.019–0.12)
(+)-**39**	Cl	S	2	212–213	$C_{25}H_{30}ClFN_4S$·2HCl	21	490	350	NT[f]
(−)-**39**	Cl	S	2	212–213	$C_{25}H_{30}ClFN_4S$·2HCl	0.75	33	67	0.041 (0.022–0.078)
40	F	S	2	174–176	$C_{25}H_{30}F_2N_4S$·dimaleate	1.7	220	110	0.039 (0.013–0.11)
(+)-**40**	F	S	2	205–206	$C_{25}H_{30}F_2N_4S$·2HCl	0.95	140	43	0.017 (0.0063–0.046)
(−)-**40**	F	S	2	205–206	$C_{25}H_{30}F_2N_4S$·2HCl	42	2900	NT	NT
(+)-**41**	Cl	O	2	179–180	$C_{25}H_{30}ClFN_4O$·dimaleate	120	1700	NT	NT
(−)-**41**	Cl	O	2	179–180	$C_{25}H_{30}ClFN_4O$·dimaleate	1.3	94	62	0.11 (0.058–0.21)
(+)-**42**	F	O	2	170–171	$C_{25}H_{30}F_2N_4O$·dimaleate	1.1	280	41	0.029 (0.0091–0.093)
(−)-**42**	F	O	2	170–171	$C_{25}H_{30}F_2N_4O$·dimaleate	57	4000	NT	NT
1 (irindalone)						3.4	400	2.6	0.58 (0.25–1.3)
44 (ritanserin)						0.40	12	47	0.10 (0.050–0.18)

[a–e] See corresponding footnotes to Table IV. [f] NT = not tested.

Table VIII. Inhitibion 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	quipazine inhibition 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 ED_{50} 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 D_2 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-HT_2 antagonists, but at the expense of higher antidopaminergic activity.[1] In order to investigate the profile of thio 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-HT_2 antagonists than **20**. However, because D_2 and α_1 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 (D_2/5-HT_2 selectivity ratios from 44 to 250 and α_1/5-HT_2 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 D_2 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 distomers (with respect to 5-HT_2 affinity) were examined for amine uptake inhibiting properties (results not shown, but IC_{50} values for inhibition of DA and NE uptake were in the range of 15–100 nM). For (+)-**20** the IC_{50} 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-HT_2 affinity varies for the enantiomeric pairs from 21 to 92. If one calculates a theoretical 5-HT_2 affinity of the distomers 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 distomers except (+)-**10** and (+)-**39** the theoretical value is still within the 95% confidence ratio (2.05 for 5-HT_2 binding, see footnote Table IV). Therefore, for these compounds it cannot be completely excluded that the observed affinity of the distomer 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 D_2 and α_1 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 D_2 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 D_2 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 D_2 receptor interaction model are also potent and stereoselective 5-HT$_2$ antagonists, we used the "D_2 conformation" of 1 in our superimposition study with ketanserin.[1] The present work does not add any data that invalidate this proposed 5-HT$_2$ 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 sties, 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 D_2 affinity[1,35] and that substituents in the 4- and 5-positions were detrimental for D_2 affinity.[35] 7-Substituted derivatives retained some D_2 affinity[35] which was confirmed in the present study (compound 12). We also knew that unsubstituted or 6-substituted compounds had high 5-HT$_2$ affinity, but the present study shows that also 4-, 5-, and 7-substituted compounds have high 5-HT$_2$ affinity. The fact that 5-substitution also is destructive for α_1 adrenoceptor affinity was the key to developing selective 5-HT$_2$ antagonists. Finally, we have shown largely parallel substitution effects in relation to D_2 and 5-HT$_2$ 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-HT$_2$, D_2, and α_1 receptor affinity are summarized in Figure 2.

Recently, a number of selective D_2 antagonists of the benzamide type have been accomodated into the D_2 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 octoclothepin 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-HT$_2$ receptor and that this pocket has a size that apparantly allows substitution in all four aromatic positions. The D_2 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 D_2 and 5-HT$_2$ receptor proteins. Further work is also in progress in order to refine the 5-HT$_2$ receptor model by conformational analyses and superimposition studies of a variety of 5-HT$_2$ 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-HT$_2$ versus 5-HT$_{1C}$ affinity touched 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.

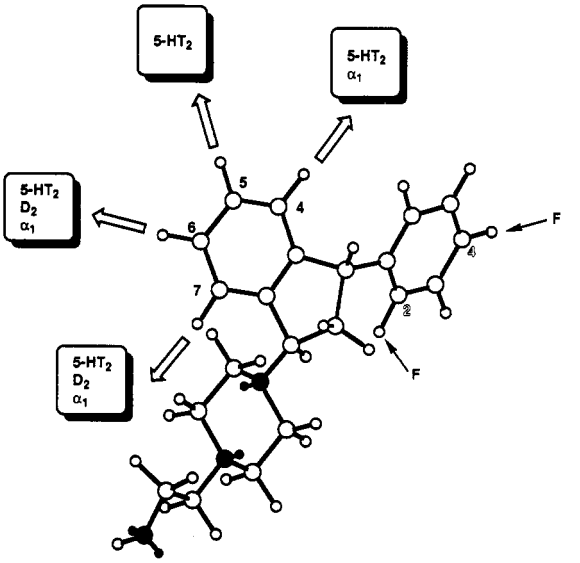


Figure 2. Summary of substitution effects in 1-piperazino-3-phenylindans (shown here with a *N*-(2-hydroxyethyl) substituent) extracted from the present paper and refs 1, 34, and 35. The compound is shown in the proposed D_2/5-HT$_2$ active conformation.[1,22,38] The consequences of substitution in the four indan benzene ring positions on affinity for 5-HT$_2$, D_2, 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.

Finally, it should be mentioned that we have recently shown that the principle of obtaining 5-HT$_2$ selectivity (versus D_2 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. ^{1}H 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, qui = 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 F_{254} precoated plates and acetone–toluene–NH_4OH–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 ±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 **13**[34] (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° (*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° (*c* 0.5, CH_3OH); ^1H NMR (base in $CDCl_3$) 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, H_3), 6.62 (dd, 1H), 6.88–7.12 (m, 5H), 7.34 (dd, 1H). Anal. ($C_{21}H_{26}Cl_2F_2N_2O$) 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° (*c* 0.5, CH_3OH); ^1H NMR (base in $CDCl_3$) identical to (+)-**13**. Anal. ($C_{21}H_{26}Cl_2F_2N_2O$) 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° (*c* 0.5, H_2O)] and (−)-**10**·dihydrochloride: mp 224–227 °C; $[\alpha]^{22}_D$ −14.1° (*c* 0.5, H_2O); ^1H NMR (base in $CDCl_3$) 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, H_3), 6.92 (s, 1H), 6.93–7.10 (m, 4H), 7.22 (dd, 1H), 7.33 (d, 1H). Anal. ($C_{21}H_{26}Cl_3FN_2O$) 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. ($C_{35}H_{42}ClFN_4O_9$) 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 °C (*c* 0.5, CH_3OH)] and 40 g (43%) of (−)-**20**·dimaleate: mp 175.0–175.3 °C; $[\alpha]^{22}_D$ −17.5° (*c* 0.5, CH_3OH), respectively. ^1H NMR (base in $CDCl_3$) 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, H_3), 6.91 (s, 1H), 6.93–7.10 (m, 4H), 7.21 (dd, 1H), 7.33 (d, 1H). Anal. ($C_{35}H_{42}ClFN_4O_9$) 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 ($MgSO_4$), 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 ($MgSO_4$), 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. ($C_{23}H_{24}ClFN_2O_4$), 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° (*c* 0.5, CH_3OH) and 1.3 g (8.0%) of (−)-**43**·maleate salt: mp 194–196 °C; $[\alpha]^{22}_D$ −30.2° (*c* 0.5, CH_3OH). Anal. ($C_{23}H_{24}ClFN_2O_4$), 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 solutiuon 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 ($MgSO_4$), 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–NH_4OH (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; $[\alpha]^{22}_D$ +6.6° (*c* 0.5, water). Anal. ($C_{25}H_{32}Cl_3FN_4S$) 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*)-pyrimidinethione·dihydrochloride, (−)-**39**: mp 212–213 °C; $[\alpha]^{22}_D$ −6.6° (*c* 0.5, water); ^{1}H NMR (base in $CDCl_3$) 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, H_3), 6.41 (br s, 1H), 6.91 (s, 1H), 6.93–7.08 (m, 4H), 7.21 (dd, 1H), 7.33 (d, 1H). Anal. ($C_{25}H_{32}Cl_3FN_4S$) 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; $[\alpha]^{22}_D$ +16.8° (*c* 0.5, water); ^{1}H NMR (base in $CDCl_3$) 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, H_3), 4.76 (br s, 1H), 6.91 (s, 1H), 6.92–7.10 (m, 4H), 7.21 (dd, 1H), 7.33 (d, 1H). Anal. ($C_{33}H_{38}ClFN_4O_9$) 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; $[\alpha]_D$ −17.2° (*c* 0.5, water). Anal. ($C_{33}H_{38}ClFN_4O_9$) 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*)-pyrimidinethione·dihydrochloride, (+)-**40**: mp 205–206 °C; $[\alpha]^{22}_D$ +26.7° (*c* 0.5, water); ^{1}H NMR (base in $CDCl_3$) 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, H_3), 6.58 (d, 1H), 6.67 (br s, 1H), 6.84–7.10 (m, 5H), 7.34 (dd, 1H). Anal. ($C_{25}H_{32}Cl_2F_2N_4S$) C, H, N.

(−)-*trans*-1-[2-[4-[5-Fluoro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-yl]piperazin-1-yl]ethyl]tetrahydro-2(1*H*)-pyrimidinethione·dihydrochloride, (−)-**40**: mp 205–206 °C; $[\alpha]^{22}_D$ −25.6° (*c* 0.5, water). Anal. ($C_{25}H_{32}Cl_2F_2N_4S$) 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; $[\alpha]^{22}_D$ +16.0° (*c* 0.5, water); ^{1}H NMR (base in $CDCl_3$) 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, H_3), 5.06 (br s, 1H), 6.60 (dd, 1H), 6.88–7.10 (m, 5H), 7.34 (dd, 1H). Anal. ($C_{33}H_{38}F_2N_4O_9$) 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; $[\alpha]^{22}_D$ −15.0° (*c* 0.5, water). Anal. ($C_{33}H_{38}F_2N_4O_9$) 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; ^{1}H NMR (the base in $CDCl_3$) 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, H_3), 6.89 (s, 1H), 6.91–7.10 (m, 4H), 7.19 (dd, 1H), 7.33 (d, 1H). Anal. ($C_{34}H_{40}ClFN_4O_{10}$) 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. ED_{50} values were calculated by log-probit analyses. IC_{50} 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 μmol/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 μmol/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 D_2 Receptors. Affinity of test compounds to dopamine D_2 receptors was estimated by their ability to displace ^{3}H-spiperone from rat striatal membranes as described by Hyttel.[46]

5-HT$_2$ Receptors. Affinity of test compounds to serotonin 5-HT$_2$ receptors was estimated by their ability to displace ^{3}H-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 ^{3}H-prazosin from whole rat brain membranes as described by Skarsfeldt and Hyttel.[47]

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