Enhanced D_1 Affinity in a Series of Piperazine Ring Substituted 1-Piperazino-3-Arylindans with Potential Atypical Antipsychotic Activity

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A study of the effect of aromatic substitution on D_1 and D_2 affinity in a series of previously reported *trans*-1-piperazino-3-phenylindans shows similar structure–activity relationships for the two receptor sites. 6-Substituted derivatives have affinity for both receptors, and 6-chloro- or 6-fluoro-substituted derivatives show preference for D_1 receptors. D_1 affinity and selectivity are significantly increased in a series of new piperazine ring substituted derivatives. Potent D_1 and D_2 antagonism in vivo are confined to derivatives with relatively small substituents in the 2-position of the piperazine ring (e.g. 2-methyl, 2,2-dimethyl, 2-spirocyclobutyl or 2-spirocyclopentyl). Consequently, the effect of aromatic substitution is examined in a series of 1-(2,2-dimethylpiperazino)-3-arylindans. All these compounds except the 4-, 5-, 7- and 4′-chloro-substituted derivatives have potent D_1 affinity (IC_{50}'s below 10 nM) and the majority of the compounds antagonize SK&F 38393-induced circling in 6-OHDA-lesioned rats with ED_{50} values about 1 μmol/kg. In vitro all compounds show preference for D_1 receptors, but in vivo they are equally effective as D_1 and D_2 antagonists. The compounds have high affinity for 5-HT_2 receptors and selected compounds show high affinity for α_1 adrenoceptors. Furthermore, a subgroup consisting of (−)-**38**, (−)-**39**, (−)-**41**, and (−)-**54** does not induce catalepsy in rats. These compounds have the potential of being "atypical" antipsychotics and have consequently been selected for further studies. The non-receptor-blocking enantiomers are shown to be inhibitors of DA and NE uptake in accordance with previous observations in compounds unsubstituted in the piperazine ring. Two compounds, (+)-**38** and (+)-**40**, block DA uptake with IC_{50} values below 10 nM. Finally, the observed structure–activity relationships are discussed in relation to previously published pharmacophore models for D_2 and 5-HT_2 receptors. It is concluded that the piperazine substituents might induce a different binding mode at the dopamine receptor sites, perhaps only at the D_1 receptor site.

Introduction

Selective dopamine (DA) D_1 antagonists and selective DA D_2 antagonists are equally effective in a number of animal models believed to be predictive for antipsychotic effects and some of the side effects of neuroleptics.[1] The antipsychotic effect of D_2 antagonists is well established and a correlation between D_2 receptor binding and "average clinical daily dose" has been demonstrated by several authors.[2–4] Whether selective D_1 antagonists have an antipsychotic effect in man is still uncertain, although preliminary results with SCH 39166 (**2b**) have been disappointing.[5]

Many antipsychotics, including the "atypical" drug clozapine (1), have affinity for both D_1 and D_2 receptors.[1,4] When D_1 and D_2 receptor binding of antipsychotic drugs belonging to different structural classes is studied in vivo, there is generally a good correspondence to the in vitro results.[4] Fluphenazine, however, becomes more D_2 selective in vivo. Antagonistic effect in vivo at D_1 or D_2 receptors can also be measured as the inhibition of the SK&F 38393- or pergolide-induced circling behavior in rats with unilateral 6-OHDA lesions, respectively.[1] Using these models, fluphenazine also becomes highly D_2 selective, while in vitro it shows equal affinity for the two receptor subtypes. The same tendency is observed for several other antipsychotics, especially from the thioxanthene or phenothiazine series. The correspondence between in vitro and in vivo results is much better for clozapine and other 6-7-6 tricyclics.[1]

When antipsychotic drugs are studied in man using positron emission tomography (PET) techniques, a similar tendency is observed for thioxanthenes and phenothiazines; i.e. they exert a lower occupancy of D_1 receptors compared to D_2 receptor occupancy than should be expected from their affinity in vitro for these receptors.[6,7] Perphenazine, for example, which has K_i values of 9.1 and 1.0 nM for the D_1 and the D_2 receptor,[1] respectively, shows at a daily dose of 8 mg 76% occupancy of D_2 receptors and 0% occupancy of D_1 receptors.[7] Likewise, thioridazine and *cis*-(Z)-flupenthixol show considerably higher D_2 than D_1 occupancy[7] although they both have equal affinity in vitro for D_1 and D_2 receptors.[1] In contrast, **1** (daily dose 125–600 mg) shows equal occupancy of D_2 (mean occupancy 47%) and D_1 (mean occupancy 44%) receptors in humans in accordance with the observed in vitro affinities.[7,8] The fact that a *lower* D_2 occupancy apparently is needed when there is a concomitant D_1 occupancy of similar magnitude led to the suggestion that the antipsychotic effect of **1** may be related to its effect in vivo on both receptor subtypes.[6]

These results in humans have been supported by animal studies estimating D_1 and D_2 occupancies.[9] Using selective antagonists it is observed that fewer D_1 than D_2 receptors have to be blocked to produce a similar antagonistic effect in a variety of test models for antipsychotic effects and side effects. With regard

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to mixed antagonists, a considerably lower occupancy at both D_1 and D_2 receptors is needed to antagonize *d*-amphetamine cue with 1 than phenothiazine and thioxanthene drugs. However, at doses that substantially block both receptor subtypes **1** is unable to induce catalepsy or block stereotyped behavior. In order to explain this it is suggested that compensatory mechanisms (i.e. effect at other receptors) may play an important role.[9]

The affinity of **1** for a multitude of receptors[10,11] (in addition to D_1 and D_2) has likewise been in focus in order to explain that 1 in patients does not produce any significant extrapyramidal side effects (and therefore has been labeled "atypical"). Especially important may be the effect on 5-HT_2 receptors and α_1 adrenoceptors. Also DA D_4 receptors have been suggested because **1** has a relatively high affinity for this DA subtype,[12] but so far this idea has not been supported by studies showing the significance of D_4 antagonism in vivo. It has been argued that a high 5-HT_2 affinity relative to D_2 affinity (as observed in **1**) should be predictive for an "atypical" profile of new antipsychotics.[13] This notion is supported by PET studies with **1** showing a high 5-HT_2 occupancy in humans (mean occupancy 89%) compared to D_2 occupancy (mean D_2 occupancy 47%).[8,14] We have recently shown that selective 5-HT_2 antagonists in an electrophysiological model can induce a partial inhibition of neurones in the ventral tegmental area (VTA), while neurones in substantia nigra pars compacta (SNC) are not affected.[15] A significant role of α_1 adrenoceptors has been demonstrated using this model by combining haloperidol with the selective α_1 antagonist prazosin. This leads to a reversal of the blockade of firing of SNC neurones (associated with the extrapyramidal side effects of the drug) but not of the VTA neurones (associated with the antipsychotic effect).[16]

All these observations suggest that compounds with "mixed" receptor profiles, such as **1**, may be promising candidates as new antipsychotic drugs. It is probably not a coincidence that risperidone[17] and the four new drugs in late clinical development (sertindole,[10] olanzapine,[11] seroquel,[11] and ziprasidone[18]) are all such "mixed" antagonists.

We have previously shown that *trans*-1-piperazino-3-phenylindans are mixed antagonists of D_2 and 5-HT_2 receptors and α_1 adrenoceptors.[19-21] We have recently shown that 5-substituted derivatives are selective 5-HT_2 antagonists.[22] During the conformational studies of these compounds we developed a receptor interaction model for D_2 antagonists.[23] By using this model a strong structural resemblance between 6-7-6 tricyclics such as dibenzothiepins, dibenzoxazepins, and dibenzodiazepins (such as **1**) and the piperazinoindans have been demonstrated by us[24,25] and others.[26] As the 6-7-6 tricyclics generally are potent D_1 antagonists,[1,25] this resemblance indicates that the indans *a priori* should have the potential for D_1 antagonism. However, until now we have reported very few data concerning the D_1 activity of these compounds. Tefludazine (**17**, Table 3) has significant affinity for the D_1 receptor, but has 100 times weaker D_1 antagonistic effect in vivo than D_2 antagonistic effect (inhibition of rotational behavior).[1] Compound **11** and three related phenylindenes and phenylindoles bind with equal potency to D_1 and D_2 receptors.[27] In this paper we present D_1 and D_2 affinities of a series of previously reported derivatives (**6-23**, Figure 1) as well as a new series of piperazine ring substituted derivatives (**24-55**, Figure 1). The goal of the project was to obtain new compounds with mixed profiles (D_1, D_2, 5-HT_2 and α_1) together with potent D_1 activity. This potency should be manifest in vivo in order to obtain a significant D_1 antagonism at least of the same magnitude as the D_2 antagonism.

Chemistry

The *trans*-1-piperazino-3-arylindan derivatives were all prepared by methods previously reported as outlined in Scheme 1.[19,21,22,24] New indanones were obtained from the corresponding 3-amino-1-cyano-3-aryl-1*H*-indene-2-carboxylic acid methyl esters produced by a method which we have published recently.[28] This method allows introduction of aromatic substituents in positions inaccessible by previously reported methods for preparation of 3-phenylindan-1-ones. The 3-arylindan-1-ols were obtained by reduction of the corresponding 3-arylindan-1-ones with sodium borohydride. Data on new enamines, indanones, and indanols are shown in Table 1. The chloroindans were obtained from the 3-arylindan-1-ols by treatment with thionyl chloride in a suitable solvent, such as ether or methylene chloride.

Alkylation of the substituted or spiro-joined piperazine derivatives with a suitably substituted 1-chloro-3-arylindan afforded a mixture of *cis*- and *trans*-1-piperazino-3-arylindans. However, the *cis*-isomer content was lower after reaction with the substituted piperazines than after reaction with unsubstituted piperazines, probably due to steric hindrance from the substituents. The isolation of the desired *trans*-isomers by fractional crystallization was therefore easier than usual. N-Methylated end products were obtained by Eschweiler-Clarke methylation. Compounds with other alkyl or hydroxyalkyl N-substituents were prepared as shown in Scheme 1.

Some of the alkylated piperazines were commercially available (2-methylpiperazine, *trans*-2,5-dimethylpiperazine, and *cis*-2,6-dimethylpiperazine). Large quantities of 2,2-dimethylpiperazine were prepared as outlined in Scheme 1. Bromination of isobutyraldehyde in dioxane afforded 2-bromoisobutyraldehyde. Alkylation of ethylenediamine with the bromoaldehyde at 5-10 °C followed by cyclization by reflux in toluene gave 2,2-dimethyl-1,2,5,6-tetrahydropyrazine. Hydrogenation over Pd/C at low pressure afforded the desired 2,2-dimethylpiperazine. 2,2-Diethylpiperazine, 5,8-diazaspiro[3.5]-nonane, 6,9-diazaspiro[4.5]decane, and 1,4-diazaspiro-[5.5]undecane were prepared by the same procedure. Octahydropyrido[1,2-*a*]pyrazine (used to prepare compound **24**) was prepared by a literature method.[29]

Only one product (apart from small amounts of *cis*-isomer) was observed in the reactions of the 2,2-disubstituted or 2,2-spiro-joined piperazines with 1-chloro-3-arylindans. For steric reasons it seemed unlikely that the product could be the 3-alkylated rather than the 2-alkylated derivative. However, to be completely sure of this difference, NOE NMR experiments were performed on compound **28**. Irradiation of the 2,2-dimethyl protons had no effect on the proton in the 1-position of the indan ring, but a profound effect on the N-methyl protons was observed. Therefore, we

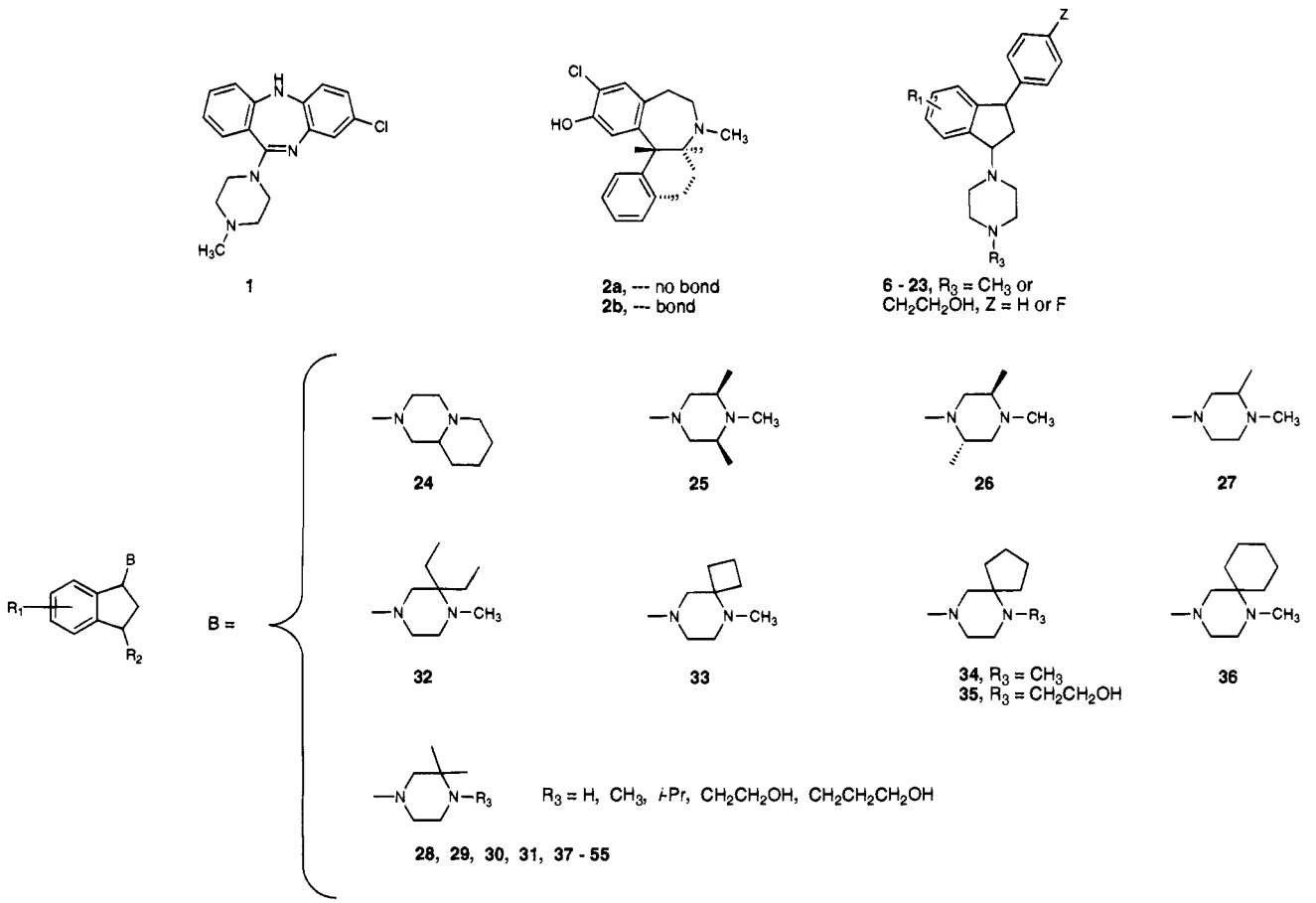


Figure 1. Structure of reference compounds and new derivatives. See Tables 3–5 for definition of R_1 and R_2.

concluded that the 2,2-dimethyl derivative as expected was formed.

Irradiation of the 2-methyl group in compound **27** also had a strong effect on the *N*-methyl group, showing that **27** is the 2-methyl and not the 3-methyl derivative.

Irradiation of the 2,6-dimethyl protons in compound **25** showed no effect on the indan ring proton in the 1-position. The commercial product used in the preparation of this compound was labeled "predominantly cis". Therefore, in addition to the difference NOE experiment, also a 2-D *J*-resolved experiment was run showing a *trans* diaxial coupling of 12 Hz of the protons in both the 2- and 6-positions. The conclusion was that the piperazine ring methyl substituents in **25** had the expected 2,6-*cis*-configuration.

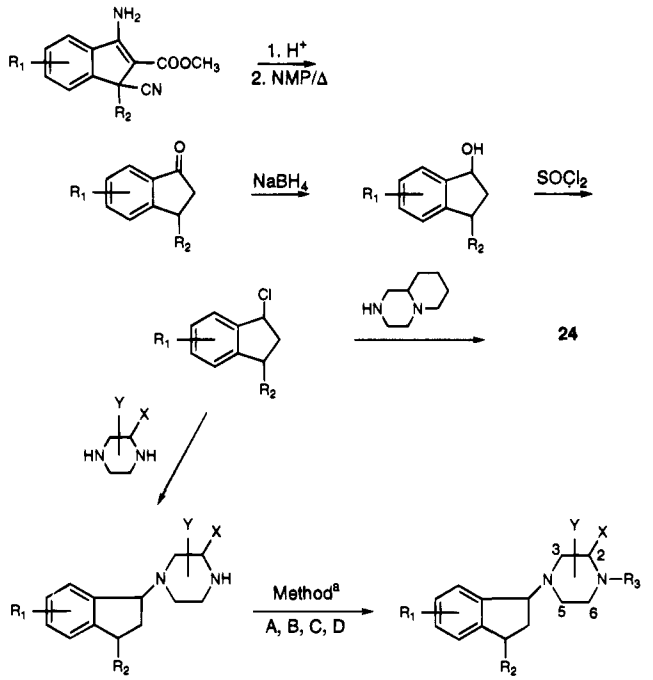
Compound **24** and **27** consist of a mixture of four *trans*-isomers due to an extra asymmetrical carbon atom in the piperazine ring. HPLC analysis of **24** confirmed that the diastereomeric mixtures were formed in an 1:1 ratio, meaning that **24** contains the same amount of all four *trans*-stereoisomers. We assume that the same is true for compound **27**.

Optical resolutions were accomplished by crystallization of diastereomeric salts of selected compounds with L-(+)- and D-(−)-tartaric acid or dibenzoyl- or di-*p*-toluoyltartaric acids. The enantiomeric purity of the resolved compounds was determined by HPLC using a chiral column. Physicochemical properties of the resolved compounds are shown in Table 2. For some compounds there seem to be discrepancies between the measured optical rotation and the calculated %ee. However, the optical rotation measurements were estimated with a precision of ±2.5%. This value only relates to the measurement itself and does not take into account errors relating to unknown impurities including residual solvents or water. The HPLC results on the other hand were obtained as the area percentage, and are therefore independent of sample purity. Absolute configurations have not been determined for any of the new compounds. Previously, the absolute configuration of (+)-*trans*-1-[2-[4-[2,3-dihydro-3-(4-fluorophenyl)-1H-inden-1-yl]-1-piperazinyl]ethyl]-2-imidazolidinone was determined by X-ray analysis to be 1*R*,3*S*.[30] Comparison of the CD spectrum of this compound with those of other resolved *trans*-1-piperazino-3-phenylindans showed consistently that the enantiomer responsible for antagonistic activity at DA and 5-HT_2 receptors and α_1 adrenoceptors had the 1*R*,3*S* configuration.[31] Therefore we assume that the eutomers in the present series also have this absolute configuration.

Results and Discussion

Structure–Activity Relationships Related to Antipsychotic Effect. Details concerning the test methods are described in the Experimental Section. In Tables 3–5 the affinities for D_1 and D_2 receptors and the D_2/D_1 selectivity index are shown. In addition, affinities for 5-HT_{2A} receptors and α_1 adrenoceptors are given for the compounds in Table 5. In Table 6 are shown D_1 and D_2 antagonistic activities in vivo for the new derivatives (measured as inhibition of SK&F 38393- and pergolide-induced circling behavior in rats with unilateral 6-OHDA lesions, respectively). The in vivo D_2/D_1 selectivity index is calculated. All compounds in Tables 4 and 5 were tested for antagonism of methyl phenidate-induced gnawing behavior in mice. This is

Scheme 1[a]



[a] (A) 2-Iodopropane/K_2CO_3 (**29**). (B) (1) Ethyl bromoacetate/K_2CO_3. (2) $LiAlH_4$ (**30**, **35**). (C) (1) Methyl malonyl chloride/TEA. (2) $LiAlH_4$ (**31**). (D) HCHO/HCOOH, all *N*-methyl derivatives.

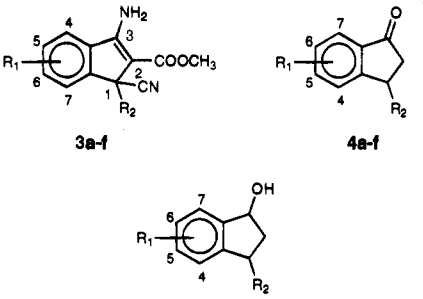
a screening test for central DA antagonistic effect in which both D_1 and D_2 antagonists are active. The cataleptogenic effect in rats was used to detect liability to induce extrapyramidal side effects. Resolved compounds were examined for effect on the inhibition of the uptake of DA, NE, and 5-HT (Table 7).

In Table 3 the D_1 and D_2 affinities of a series of previously reported compounds are shown.[19-22,24] Derivatives which are unsubstituted or have a 6-fluoro or 6-chloro substituent have higher affinity for D_1 than for D_2 receptors, while derivatives with other 6-substituents (**16**-**23**) have preference for D_2 receptors. It is also seen that the D_1 affinity of compounds bearing a substituent in the 6-position varies much more (8.3−690 nM) than the D_2 affinity (8.1−91 nM). This indicates that the D_1 receptor interaction site might be more sensitive to the nature of the indan phenyl ring substituent.

As previously discussed[22,24] substitution in the 4- or 5-position is detrimental for D_2 affinity. The same phenomenon is observed for the D_1 receptor. Some D_1 affinity is observed for the 7-chloro-substituted derivative **15**, although the consequence of moving the chloro atom from the 6- to the 7-position is much more dramatic for D_1 than for D_2 affinity.

Having observed that a good D_1 affinity was confined to 6-fluoro- or 6-chloro-substituted derivatives, we decided to examine the effect of various substitutions in the piperazine ring in a series of 6-chloro-substituted derivatives (Table 4). The idea for making changes in

Table 1. Structure and Physicochemical Data of New 3-Aminoindenes (**3**), 1-Indanones (**4**), and 1-Indanols (**5**)[a]



type	R_1 - 3	R_1 - 4/5	R_2
a	5-Cl	6-Cl	phenyl
b	5-Cl	6-Cl	2-fluorophenyl
c	5-Cl	6-Cl	3-fluorophenyl
d	5-Br	6-Br	4-fluorophenyl
e	4-F	7-F	4-fluorophenyl
f	5-Cl	6-Cl	3-thienyl

compd	mp, °C	(re)crystn solv[b]	yield (%)	formula[c]
3b	207−209	IPE	72	$C_{18}H_{12}ClFN_2O_2$
3d	177−180	IPE	67	$C_{18}H_{12}BrFN_2O_2$
3f	207−209	T	41	$C_{16}H_{11}ClN_2O_2S$
4a	94−96	C	59	$C_{15}H_{11}ClO$
4b	89−92	IPE	40	$C_{15}H_{10}ClFO$
4c	73−75	C	53	$C_{15}H_{10}ClFO$
4d	90−92	IPE/E	57	$C_{15}H_{10}BrFO$
4e	111−113	IPE	87	$C_{15}H_{10}F_2O$
4f	79−81	C	56	$C_{13}H_9ClOS$
5a	95−97	C	88	$C_{15}H_{13}ClO$
5b	88−89	P	65	$C_{15}H_{12}ClFO$
5c	101−103	P	83	$C_{15}H_{12}ClFO$
5d	140−142	C	90	$C_{15}H_{12}BrFO$
5e	79−80	C	79	$C_{15}H_{12}F_2O$
5f	87−89	C	80	$C_{13}H_{11}ClOS$

[a] Data for the 3-aminoindenes **3a**, **3c**, and **3e** have previously been reported in ref 28. [b] C = cyclohexane, E = ether, IPE = isopropyl ether, P = pentane, T = toluene. [c] Anal. C, H, N.

the piperazine ring came from our experience with neuroleptics of the thioxanthene type. During our work with thioxanthenes, we observed that certain *Z*-isomers of thioxanthenes with a bicyclic octahydro-2*H*-quinolizin-2-ylidene group in the 9-position showed a good D_1 selectivity in vitro.[32a] The "piperazine analogue" of octahydro-2*H*-quinolizine is octahydropyrido[1,2-*a*]pyrazine. Although the conformational flexibility of the indan derivative is very different from that of the thioxanthene derivatives, we decided to make this compound (**24**, Table 4). This derivative has 4−5-fold increased affinity for D_1 receptors compared with the simple piperazine analogue 11, while the D_2 affinity is unaffected. However, due to an extra chiral carbon atom in the bicyclic side chain, **24** is a mixture of four *trans*-isomers. The compound shows also side effect potential (catalepsy, Table 6) and is therefore overall not attractive. The *cis*-2,6-dimethylated derivative **25** shows a good D_1 selectivity, but has no effects in vivo. The *trans*-2,5-dimethylated derivative **26** has lower affinity and marginally improved selectivity compared to **11**.

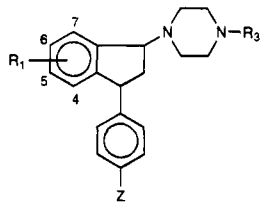
Interestingly, the simple 2-methylpiperazine derivative **27** has similar receptor affinity and selectivity as

Table 2. Data on Resolved Compounds

compd	resolving agent[a]	(re)crystn solv[b]	yield (%)[c]	$[\alpha]^t_D$,[d] deg	c,[e] solvent	optical purity[f] (%ee)
(−)-**28**	(+)-DBT	Ac	31	−23.4	0.5, MeOH	94.5 (85.4)[g]
(+)-**28**	(−)-DBT	Ac	35	+24.5	0.5, MeOH	99.6 (99.7)[g]
(−)-**29**	(+)-DBT	EtOH/E	43	−18.4	1.0, DMF	98.4
(+)-**29**	(−)-DBT	EtOH/E	40	+18.2	1.0, DMF	99.8
(−)-**34**	(+)-DTT	MeOH/Ac	17	−13.8	1.0, DMF	75.3
(+)-**34**	(−)-DTT	MeOH/Ac	37	+10.5	1.0, DMF	61.0
(−)-**35**	(+)-DBT	MeOH/Ac/E	11	−10.2	1.0, MeOH	99.7
(+)-**35**	(−)-DBT	MeOH/Ac/E	20	+10.7	1.0, MeOH	94.3
(−)-**38**	(+)-DTT	*n*-PrOH	22	−22.0	0.5, MeOH	95.4
(+)-**38**	(−)-DTT	*n*-PrOH	24	+22.2	0.5, MeOH	93.6
(−)-**39**	(+)-DTT[h]	Ac/Me/OH	18	−2.7	0.5, MeOH	100
(+)-**39**	(−)-DTT[h]	Ac/MeOH	18	+2.5	0.5, MeOH	100
(−)-**40**	(+)-DTT[h]	Ac	5.7	−3.8	0.5, MeOH	100
(+)-**40**	(−)-DTT[h]	Ac	8.0	+3.8	0.5, MeOH	100
(−)-**41**	(−)-T	Ac/MeOH	27	−25.5	0.5, MeOH	99.6
(+)-**41**	(+)-T	Ac/MeOH	30	+25.3	0.5, MeOH	95.0
(−)-**54**	(+)-T	EtOH	28	−30.4	0.5, MeOH	99.6
(+)-**54**	(−)-T	EtOH	25	+31.2	0.5, MeOH	94

[a] (+)-DBT = dibenzoyl-D-tartaric acid, (−)-DBT = L-isomer, (+)-DTT = di-*p*-toluoyl-D-tartaric acid, (−)-DTT = L-isomer, (−)-T = D-tartaric acid, (+)-T = L-tartaric acid. [b] (Re)crystn solvent, final salt, Ac = acetone, E = ether, EtOH = ethanol, MeOH = methanol, *n*-PrOH = *n*-propanol. [c] Yield of final salt relative to amount of racemic starting material. [d] *t* = room temperature. [e] c = concentration (in %). [f] HPLC conditions, see Experimental Section. [g] Number in parenthesis is %ee of batch I. [h] Used for resolution of secondary amine derivatives that subsequently were methylated (see Experimental Section).

Table 3. D_1 and D_2 Affinity of Previously Reported *trans*-1-Piperazino-3-phenylindans[a]



				receptor binding[b]		
compd	R_1	Z	R_3	D_1	D_2	D_2/D_1
6[c]	H	H	CH_3	480	690	1.4
7	H	H	CH_2CH_2OH	730	2800	3.8
8	6-F	F	CH_3	12	91	7.6
(+)-**8**	6-F	F	CH_3	5.3	31	5.8
(−)-**8**	6-F	F	CH_3	2800	410	0.15
9	6-F	F	CH_2CH_2OH	16	82	5.1
10	6-Cl	H	CH_3	16	61	3.8
11[c]	6-Cl	F	CH_3	9.5	12	1.3
12	4-Cl	F	CH_2CH_2OH	2000	220	0.11
13	5-Cl	F	CH_2CH_2OH	1800	2200	1.2
14	6-Cl	F	CH_2CH_2OH	8.3	20	2.4
15	7-Cl	F	CH_2CH_2OH	130	46	0.4
16[c]	6-CF_3	F	CH_3	17	8.1	0.5
17	6-CF_3	F	CH_2CH_2OH	23	10	0.4
18[c]	6-CH_3	F	CH_3	38	13	0.4
19	6-CH_3	F	CH_2CH_2OH	51	23	0.5
20	6-*i*-Pr	F	CH_2CH_2OH	66	14	0.2
21	6-OCH_3	F	CH_2CH_2OH	210	86	0.4
22	6-SCH_3	F	CH_2CH_2OH	39	13	0.3
23	6-SO_2CH_3	F	CH_2CH_2OH	690	42	0.06

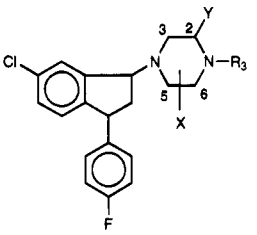
[a] The compounds have previously been reported in the refs 19–22 and 24. [b] Results are expressed as IC_{50} values in nM and they are the mean of at least two determinations. Two full concentration–effect curves were measured by using five concentrations of test drug in triplicate (covering three decades). Standard deviation ratios were obtained by calculating the variance of repeated measures of ratios between the first and the second determination for a series of 100 drugs. If the ratio was greater than three times the SD (99% confidence interval), extra determinations were performed and outliers were discarded. The following 95% confidence ratios (2SD) were calculated: D_1, 2.13; D_2, 2.26. [c] Compounds **6**, 11, **16**, and 18: Anal. C, H, N (previously only reported in patent literature).

24. In vivo it is a very potent antagonist of both SK&F 38393- and pergolide-induced rotational behavior. Despite the fact that the D_1 selectivity is lower in vivo, the potency of **24** as a D_1 antagonist is remarkably high. However, the cataleptogenic activity of the compound is rather low compared to its DA receptor blocking activity.

However, like **24**, **27** is a mixture of four *trans*-isomers. An obvious way to attack this problem is to add an extra methyl group in the 2-position, as in **28**. This compound shows a high D_1 selectivity in vitro and has the best profile so far. The general tendency toward lower D_1 selectivity in vivo is also seen with this compound (Table 6), but a selectivity ratio of 2 in vivo is still very unusual. The cataleptogenic potential is also relatively low. Therefore, we decided to resolve the compound. The activity of the enantiomers (−)-**28** and (+)-**28** is in accordance with our previous experience with resolved 1-piperazino-3-phenylindans;[19–22] i.e., all the receptor blocking activity resides in one enantiomer while the other enantiomer is a DA/NE uptake inhibitor (Table 7). Compound (−)-**28** is close to the goal of obtaining mixed antagonists (see also Table 5) with potent D_1 antagonistic activity in vivo. However, we were still interested to determine whether the profile could be further improved. We decided to concentrate on symmetrically 2,2-disubstituted derivatives without an additional chiral center.

2,2-Dimethylated compounds with N-substituents other than methyl (**29**–**31**) have no improved profile (**31** has a high D_2/D_1 ratio but is more cataleptogenic than **28**). The 2,2-diethyl derivative **32** and the spirocyclohexyl derivative **36** have lower D_1 affinity and selectivity than **28** and are inactive in vivo. In contrast spiro-joined derivatives with 4- or 5-membered rings show potent activity (**33**–**35**). Both **33** and **34** have a profile close to that of **28**. In vivo, **34** has an exceptionally good D_1 selectivity. It was only possible to obtain a partial resolution of **34** (see Table 2) but the purity of the receptor blocking enantiomer (−)-**34** (75.3% ee) is high enough to demonstrate that the high selectivity is not retained in the enantiomer. The D_1/D_2 affinity of (+)-**34** is clearly due to its content of the (−)-enantiomer. The profile of (−)-**35**, the N-hydroxyethyl derivative of (−)-**34**, is not better than that of (−)-**28**.

Table 4. Variations of the Piperidine Ring in a Series of *trans*-1-Piperazino-3-(4-fluorophenyl)-6-chloroindans[a]



compd	X	Y	R_3	mp (°C)	formula[b]	receptor binding[c] D_1	D_2	D_2/D_1
24	H	$-(CH_2)_4-$		172–174	$C_{23}H_{26}ClFN_2$·dimaleate	2.1	11	5.2
25	6-CH_3	CH_3	CH_3	158–160	$C_{22}H_{26}ClFN_2$·dioxalate	13	120	9.2
26	5-CH_3	CH_3	CH_3	166–169	$C_{22}H_{26}ClFN_2$·dimaleate	19	41	2.2
27	H	CH_3	CH_3	181–183	$C_{21}H_{24}ClFN_2$·dimaleate	2.4	12	5
28	2-CH_3	CH_3	CH_3	143–146	$C_{22}H_{26}ClFN_2$·maleate	1.3	25	19
(−)-**28**	2-CH_3	CH_3	CH_3	202–204	$C_{22}H_{26}ClFN_2$·dihydrochloride	0.68[d]	5.0[d]	7.4
(+)-**28**	2-CH_3	CH_3	CH_3	203–205	$C_{22}H_{26}ClFN_2$·dihydrochloride	620[d]	>1000[d]	
29	2-CH_3	CH_3	*i*-Pr	157–159	$C_{24}H_{30}ClFN_2$·dioxalate·0.8H_2O	0.82	5.0	6.1
(−)-**29**	2-CH_3	CH_3	*i*-Pr	169–171	$C_{24}H_{30}ClFN_2$·dioxalate	0.66	3.1	4.7
(+)-**29**	2-CH_3	CH_3	*i*-Pr	171–172	$C_{24}H_{30}ClFN_2$·dioxalate	52	NT	
30	2-CH_3	CH_3	$(CH_2)_2OH$	79–81	$C_{23}H_{28}ClFN_2O$	1.0	3.0	3.0
31	2-CH_3	CH_3	$(CH_2)_3OH$	100–104	$C_{24}H_{30}ClFN_2O$·dioxalate	1.1	21	19
32	2-Et	Et	CH_3	144–146	$C_{24}H_{30}ClFN_2$·oxalate	8.8	38	4.3
33		2-[$-(CH_2)_3-$]	CH_3	188–190	$C_{23}H_{26}ClFN_2$·dihydrochloride·0.5H_2O	0.89	6.3	7.1
34		2-[$-(CH_2)_4-$]	CH_3	144–147	$C_{24}H_{28}ClFN_2$·fumarate	0.85	10	12
(−)-**34**		2-[$-(CH_2)_4-$]	CH_3	204–206	$C_{24}H_{28}ClFN_2$·dihydrochloride	0.96	4.5	4.7
(+)-**34**		2-[$-(CH_2)_4-$]	CH_3	205–207	$C_{24}H_{28}ClFN_2$·dihydrochloride·0.4H_2O	6.6	20	3.0
35		2-[$-(CH_2)_4-$]	$(CH_2)_2OH$	167–169	$C_{25}H_{30}ClFN_2O$·1.8 hydrochloride	1.9	13	6.8
(−)-**35**		2-[$-(CH_2)_4-$]	$(CH_2)_2OH$	197–200	$C_{25}H_{30}ClFN_2O$·dihydrobromide·0.6H_2O	1.0	5.0	5.0
(+)-**35**		2-[$-(CH_2)_4-$]	$(CH_2)_2OH$	206–208	$C_{25}H_{30}ClFN_2O$·dihydrobromide·0.6H_2O	51	NT[e]	
36		2-[$-(CH_2)_5-$]	CH_3	205–207	$C_{25}H_{30}ClFN_2$·dihydrochloride	6.0	24	4

[a] Isomeric purity >97% *trans*-isomer, except **26** (84%), **31** (94%), and **33** (94%). [b] Anal. C, H, N. [c] See footnote *b* to Table 3. [d] Results obtained with batch I (see Table 2). [e] NT = not tested.

We concluded that only 2,2-disubstitution of limited size (i.e. dimethyl, spirocyclobutyl, or spirocyclopentyl) is allowed in order to retain good selectivity and in vivo activity.

We could not be certain that the structure–activity relationships with respect to variation in aromatic substitution would be similar in the piperazine ring substituted derivatives to the derivatives without piperazine substituents shown in Table 3. Accordingly, we made the series of 2,2-dimethylated derivatives shown in Table 5.

It is clear that the 2,2-dimethyl substitution of the piperazine ring in itself has a dramatic effect on the D_1 affinity as the unsubstituted derivative **37** has 37 times higher D_1 affinity than **6**. As the D_2 affinity only increases 5 times, **37** is also much more D_1 selective than **6**. This general increase in D_1 affinity due to the 2,2-dimethyl substitution is observed for all the compounds in Table 5, giving them all (except **45**) a D_2/D_1 ratio greater than 1. Even the 4- and 5-chloro-substituted derivatives **47** and **48** retain a significant D_1 affinity compared to their unmethylated counterparts **12** and **13**. In this series a 7-chloro substituent (**49**) completely destroys the D_2 affinity, while a respectable D_1 affinity remains. Consequently, **49** has a high D_1 selectivity in vitro. The 7-fluoro derivative **50** has considerably higher affinity for both receptors and is D_1 selective in vitro, but not in vivo.

We have previously observed that D_2 affinity is preserved in compounds with a 2′-fluoro substituent on the 3-phenyl ring.[24] This is also seen here (**51**) and the D_1 affinity is also comparable to that of the 4′-fluoro counterpart (**28**). However, in vivo **51** is much less active than **28**. The D_2 affinity of the 3′-fluoro-substituted derivative **52** is low. A similar, low affinity was also observed for the corresponding *N*-(2-hydroxyethyl)piperazine derivative.[24] Compound **52** still has significant D_1 affinity, but the activity is lost in vivo. A 4′-chloro substitution (**53**) is clearly destructive for activity both in vitro and in vivo as previously observed in other 4′-chloro derivatives.[19,21,22,24]

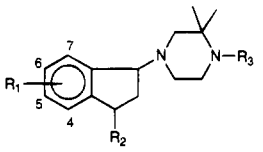
We have not previously reported on 3-thienyl derivatives of 1-piperazinoindans, but it is obvious—by comparison of (−)-**41** with (−)-**54** and of **28** with **55**—that the 3-thienyl group is at least as effective a 3-substituent as a 4′-fluorophenyl ring.

It is noteworthy that the 6-unsubstituted derivative **39** and its active enantiomer (−)-**39** have potent D_1 and D_2 activity both in vitro and in vivo. We have previously observed that similar unsubstituted derivatives (without the 2,2-dimethyl piperazine substituents) have very low D_2 affinity and no neuroleptic activity.[19,21] Also **38** and (−)-**38** have unusually potent effects both in vitro (compare with **10**) and in vivo, despite the lack the 4′-fluoro atom, which we previously have reported to be necessary in order to obtain a potent effect in vivo.[19,24]

The secondary piperazine derivatives **41**, (−)-**41**, **43**, **45**, **54**, and (−)-**54** and corresponding N-methylated derivatives have very similar receptor affinities. Although the secondary amines have marginally weaker DA antagonistic effects in vivo, it is interesting that they do not induce catalepsy in contrast to their N-methylated counterparts (**28**, (−)-**28**, **44**, **46**, and **55**).

The remaining compounds (**40-46**) are all 6-substituted/4′-fluoro-substituted derivatives. They all have potent D_1 and D_2 affinity, with selectivity ratios ≥1. In vivo

Table 5. Aromatic Substitution Effects in *trans*-1-(2,2-Dimethylpiperazino)-3-arylindans[a]



compd	R_1	R_2	R_3	mp (°C)	formula[b]	receptor binding[c] D_1	D_2	5-HT_{2A}	α_1	D_2/D_1
37	H	Ph[d]	CH_3	162–165	$C_{22}H_{28}N_2$·dimaleate	13	140	21	NT[e]	11
38	6-Cl	Ph	CH_3	170–171	$C_{22}H_{27}ClN_2$·1.5maleate	1.6	20	3.2	23	13
(−)-**38**	6-Cl	Ph	CH_3	196–197	$C_{22}H_{27}ClN_2$·fumarate	1.1	9.5	4.4	10	8.6
(+)-**38**	6-Cl	Ph	CH_3	196–197	$C_{22}H_{27}ClN_2$·fumarate	15	260	68	NT	17
39	H	4-F-C_6H_4	CH_3	135–137	$C_{22}H_{27}FN_2$·dimaleate	3.0	29	5.1	NT	10
(−)-**39**	H	4-F-C_6H_4	CH_3	197–199	$C_{22}H_{27}FN_2$·fumarate	2.5	12	2.9	4.4	4.8
(+)-**39**	H	4-F-C_6H_4	CH_3	198–199	$C_{22}H_{27}FN_2$·fumarate	250	4900	650	NT	20
40	6-F	4-F-C_6H_4	CH_3	154–156	$C_{22}H_{26}F_2N_2$·dimaleate	0.88	11	3.6	12	13
(−)-**40**	6-F	4-F-C_6H_4	CH_3	178–180	$C_{22}H_{26}F_2N_2$·fumarate	0.71	6.8	1.9	4.7	10
(+)-**40**	6-F	4-F-C_6H_4	CH_3	178–180	$C_{22}H_{26}F_2N_2$·fumarate	88	1500	360	NT	17
41	6-Cl	4-F-C_6H_4	H	242–244	$C_{21}H_{24}ClFN_2$·hemifumarate	2.1	7.3	3.2	39	3.5
(−)-**41**	6-Cl	4-F-C_6H_4	H	157–160	$C_{21}H_{24}ClFN_2$·fumarate	1.1	9.0	3.7	12	8
(+)-**41**	6-Cl	4-F-C_6H_4	H	157–160	$C_{21}H_{24}ClFN_2$·fumarate	1100	12000	3600	NT	11
28	6-Cl	4-F-C_6H_4	CH_3			1.3	25	2.1	4.9	19
(−)-**28**	6-Cl	4-F-C_6H_4	CH_3			0.68	5.0	1.1	3.9	7.4
42	6-Br	4-F-C_6H_4	CH_3	142–145	$C_{22}H_{26}BrFN_2$·1.5fumarate	1.8	8.6	3.0	NT	4.8
43	6-CF_3	4-F-C_6H_4	H	94–95	$C_{22}H_{24}F_4N_2$	2.8	5.2	7.5	NT	1.9
44	6-CF_3	4-F-C_6H_4	CH_3	112–114	$C_{23}H_{26}F_4N_2$	1.5	5.7	4.5	NT	3.8
45	6-CH_3	4-F-C_6H_4	H	108–110	$C_{22}H_{27}FN_2$	5.9	5.6	1.5	NT	0.95
46	6-CH_3	4-F-C_6H_4	CH_3	119–121	$C_{23}H_{29}FN_2$	2.1	4.8	3.4	NT	2.3
47	4-Cl	4-F-C_6H_4	CH_3	120–125	$C_{22}H_{26}ClFN_2$·dioxalate	45	55	29	NT	1.2
48	5-Cl	4-F-C_6H_4	CH_3	126–128	$C_{22}H_{26}ClFN_2$	37	340	9.3	94	9.2
49	7-Cl	4-F-C_6H_4	CH_3	153–155	$C_{22}H_{26}ClFN_2$·1.3oxalate	32	1200	31	NT	38
50	7-F	4-F-C_6H_4	CH_3	133–135	$C_{22}H_{26}F_2N_2$·oxalate	3.8	74	9.8	15	19
51	6-Cl	2-F-C_6H_4	CH_3	154–156	$C_{22}H_{26}ClFN_2$·dimaleate	4.4	36	21	NT	8.2
52	6-Cl	3-F-C_6H_4	CH_3	140–142	$C_{22}H_{26}ClFN_2$·dimaleate	9.6	280	26	NT	29
53	6-Cl	4-Cl-C_6H_4	CH_3	91–93	$C_{22}H_{26}Cl_2N_2$·dioxalate·0.5H_2O	34	63	32	NT	1.9
54	6-Cl	3-thienyl	H	163–165	$C_{19}H_{23}ClN_2S$·dimaleate	1.4	8.2	1.0	NT	5.9
(−)-**54**	6-Cl	3-thienyl	H	210–211	$C_{19}H_{23}ClN_2S$·hemifumarate	0.84	7.1	1.9	25	8.5
(+)-**54**	6-Cl	3-thienyl	H	210–211	$C_{19}H_{23}ClN_2S$·hemifumarate	440	6700	1100	NT	15
55	6-Cl	3-thienyl	CH_3	173–176	$C_{20}H_{25}ClN_2S$·2HCl·0.7H_2O	0.76	6.1	1.7	14	8.0
1	Clozapine					130	330	7.8	9.2	2.5
2a	SCH 23390					0.37	3200	14	970	8650

[a] Isomeric purity ≥95% *trans* except for **42** (89%) and **53** (92%). [b] Anal. C, H, N. [c] See footnote *b* in Table 3. 95% confidence ratios for 5-HT_{2A}, 2.05; α_1, 2.20. [d] Ph = phenyl. [e] NT = not tested.

43 and **45** failed to show D_1 antagonistic activity, while the other compounds are effective antagonists of both receptors with varying selectivity ratios.

The compounds in Table 5 have 5-HT_{2A} affinities of largely the same magnitude as the D_1 affinity. The active enantiomers of **28**, **38**–**41**, and **54** were all potent, long-acting 5-HT_2 antagonists in vivo (antagonism of quipazine-induced head-twitch syndrome[33]) with ED_{50} values after 24 h between 0.02 and 0.5 μmol/kg. The most interesting compounds have also been tested for affinity for 5-HT_{2C} receptors ([^{3}H]mesulergine binding to cloned rat 5-HT_{2C} receptors expressed in NIH-3T3 cells, see the Experimental Section). The 5-HT_{2C} receptor affinity is of similar magnitude as the 5-HT_{2A} affinity, but with a tendency of being stronger for the secondary amines, as also observed for the secondary amine of **1**[34] (IC_{50}'s for (−)-**38**, (−)-**39**, (−)-**41**, and (−)-**54** are 1.7, 11, 0.17, and 0.28 nM, respectively). As shown in Table 5, the same enantiomers have also potent affinity for α_1 adrenoceptors.

In conclusion, the (−)-enantiomers of **38**, **39**, **41**, and **54** are potent D_1/D_2 antagonists. They show some D_1 selectivity in vitro while in vivo they are equipotent as D_1 and D_2 antagonists. They are potent 5-HT_2 antagonists and have high affinity for α_1 adrenoceptors. Finally, they do not induce catalepsy. They fulfill the goal of being mixed antagonists with the potential of having "atypical" antipsychotic effect and are accordingly selected for further preclinical studies.

DA/NE Uptake Inhibition. We have previously reported that 1*S*,3*R* enantiomers of *trans*-1-piperazino-3-phenylindans generally are inhibitors of DA and NE uptake.[19–22] The non-receptor-blocking enantiomers in the present series were therefore tested for inhibition of DA, NE, and 5-HT uptake (Table 7). As already mentioned above for **28**, the new derivatives follow the general pattern; i.e. the (+)-enantiomers are inhibitors of DA and NE uptake, but not of 5-HT uptake. All the 2,2-dimethylated enantiomers have potent affinity for the uptake sites while the two spiro derivatives show low affinity. This indicate that only substituents of limited size are allowed at the uptake sites. On the other hand, (+)-**40** has more than 10 times higher affinity for the DA uptake site than its unmethylated analogue (−)-**8**. This potency is comparable to some of the most potent 3′,4′-dichloro-substituted derivatives reported previously.[19,20] In relation to structure–activity discussions above concerning racemic compounds, it is important to note that even potent inhibition of DA uptake as in (+)-**40** apparently does not influence the in vivo activity of the racemate i.e. the receptor blocking enantiomers are all twice as potent as the racemates.

Table 6. DA-Antagonistic Effects of Compounds *In Vivo*[a]

compd	inhibition of rotational behavior		methyl phenidate antagonism	catalepsy	D_2/D_1
	SKF 38393 (D_1)	pergolide (D_2)			
24	NT	NT	14 (7.4–26)	4.1 (2.9–5.7)	
25	>18	>18	53 (31–90)	>36	
26	>17	4.1 (2.2–7.8)	>66	>33	<0.2
27	0.32 (0.15–0.67)	0.47 (0.25–0.89)	0.27 (0.12–0.59)	9.3 (6.6–13)	1.5
28	0.59 (0.26–1.4)	1.2 (0.63–2.3)	0.65 (0.31–1.4)	25 (18–35)	2.0
(−)-**28**	0.26 (0.11–0.60)	0.62 (0.31–1.2)	0.48 (0.32–0.72)	9.8 (7.5–13)	2.4
29	1.0 (0.63–1.6)	1.0 (0.35–2.9)	1.6 (0.89–2.9)	6.9 (4.3–11)	1.0
(−)-**29**	0.50 (0.25–1.0)	0.74 (0.35–1.6)	0.76 (0.51–1.1)	7.1 (5.1–9.9)	1.5
30	0.63 (0.35–1.1)	0.10 (0.03–0.37)	0.34 (0.23–0.51)	3.7 (2.8–4.8)	0.16
31	0.30 (0.15–0.60)	0.65 (0.28–1.5)	NT	<17	2.2
32	NT	NT	>81	>20	
33	0.49 (0.22–1.1)	2.0 (0.44–9)	1.0 (0.77–1.3)	69 (49–97)	4.1
34	1.1 (0.38–3.2)	18 (4.1–79)	1.7 (1.2–2.4)	42 (16–109)	16
(−)-**34**	1.3 (0.50–3.4)	5.5 (3.4–8.8)	1.2 (0.85–1.7)	31 (24–40)	4.2
35	0.65 (0.22–2.0)	2.4 (0.8–7.2)	1.6 (1.0–2.6)	14 (4.7–42)	3.7
(−)-**35**	0.25 (0.10–0.63)	0.33 (0.14–0.79)	0.49 (0.26–0.91)	2.7 (1.3–5.7)	1.3
36	NT	NT	>80	NT	
37	NT	NT	>36	>36	
38	4.5 (3.2–6.3)	13 (6.2–27)	24 (14–41)	>76	2.9
(−)-**38**	2.6 (0.61–11)	3.3 (1.7–6.6)	8.8 (4.4–18)	>85	1.3
39	1.6 (0.61–3.5)	4.1 (2.1–8.2)	12.0 (8.6–17)	>70	2.6
(−)-**39**	1.4 (0.88–2.2)	1.3 (0.26–6.5)	7.2 (3.3–16)	>44	0.93
40	0.50 (0.25–1.0)	1.1 (0.44–2.8)	2.1 (0.91–4.8)	>68	2.2
(−)-**40**	0.17 (0.09–0.31)	0.18 (0.04–0.94)	1.0 (0.40–2.5)	42 (30–59)	1.1
41	3.5 (1.7–7.4)	9.2 (7.1–12)	6.7 (3.9–11)	>48	2.6
(−)-**41**	1.4 (0.74–2.7)	1.0 (0.45–2.2)	5.6 (2.5–12)	>84	0.71
42	1.0 (0.59–1.7)	1.3 (0.77–2.2)	1.5 (0.63–3.6)	9.4 (5.0–18)	1.3
43	>26	4.0 (1.1–15)	2.7 (1.4–5.4)	>51	<0.15
44	3.9 (2.0–7.8)	1.2 (0.6–2.4)	0.99 (0.62–1.6)	5.2 (3.3–8.3)	0.31
45	>29	5.2 (2.9–9.4)	33 (14–76)	>29	<0.18
46	2.7 (1.1–6.8)	3.5 (1.9–6.3)	1.4 (0.93–2.1)	33 (16–69)	1.3
47	NT	NT	>36	NT	
48	NT	NT	>110	NT	
49	NT	NT	>41	>41	
50	6.4 (3.8–11)	5.9 (3.0–12)	6.9 (3.1–15)	>90	0.92
51	>17	19 (8.3–44)	34 (15–78)	>33	<1.1
52	>33	>33	>33	>33	
53	NT	NT	>69	NT	
54	6.0 (4.3–8.4)	6.6 (2.1–20)	6.5 (2.6–16)	>35	1.1
(−)-**54**	1.9 (1.1–3.4)	2.1 (1.1–4.0)	11 (5.0–24)	>49	1.1
55	0.72 (0.36–1.4)	0.73 (0.35–1.5)	1.3 (0.72–2.3)	44 (22–88)	1.0
1	8.0 (3.3–19)[c]	3.7 (1.4–9.5)[c]	98 (70–137)	>120	0.46
2a	0.0061 (0.0030–0.013)[c]	>14[c]	0.36 (0.18–0.72)	2.9 (1.1–7.5)	>2000

[a] Results are expressed as ED_{50} values in μmol/kg (sc); 95% confidence limits in parentheses. [b] NT = not tested. [c] Drug pretreatment time 1 h.

Table 7. Uptake Inhibition of Resolved Compounds

compd	inhibition of [^{3}H]amine uptake[a]		
	DA	NE	5-HT
(+)-**8**[b]	1700	12000	3900
(−)-**8**[b]	81	28	610
(−)-**28**	3200	6500	7200
(+)-**28**	16	68	>1000
(−)-**29**	1300	5600	3500
(+)-**29**	20	100	2600
(+)-**34**	150	690	1800
(+)-**35**	120	440	2400
(−)-**38**	390	1700	4000
(+)-**38**	7.5	26	5300
(−)-**39**	5200	17000	10000
(+)-**39**	25	76	5200
(−)-**40**	4000	>10000	12000
(+)-**40**	7.1	20	3700
(−)-**41**	400	2200	1800
(+)-**41**	29	290	>100
(−)-**54**	2700	4000	4500
(+)-**54**	27	73	2000

[a] IC_{50}, nM. The following 95% confidence ratios (2SD) were calculated: DA uptake, 2.76; NE uptake, 2.68; 5-HT uptake, 2.04 (see also footnote *b* in Table 3). [b] Previously reported in refs 19 and 20.

Conformational Properties and Receptor Interactions. In our previous studies of mixed D_1/D_2 antagonists such as the enantiomers of octoclothepin,[25] compound 11, and three related phenylindenes and phenylindoles[27] we concluded that they may bind to the D_1 receptor in essentially the same conformation as the proposed biologically active conformation of these compounds at the D_2 receptor. Froimowitz and co-workers have made the same suggestion based on studies of further mixed D_1/D_2 antagonists including 6–7–6 tricyclics[26] as well as thioxanthenes and phenothiazines.[35] It has not yet been possible to fit selective D_1 antagonists such as **2a** and **2b** into this "combined" D_1/D_2 receptor model in a way that satisfactory explains the complete loss of D_2 affinity in these compounds. Froimowitz and Cody have made a qualitative proposal for a fit of **2b** to the model explaining its D_1 selectivity by the presence of its unsubstituted phenyl ring in a space unoccupied by D_2 antagonists.[35] However, more extensive studies are clearly needed in order to confirm or reject this hypothesis.

Palm has made conformational studies in relation to the D_2 receptor model of compounds **24-28** in the present series.[32b] Except for **26**, the substituents in the piperazine ring cannot interact with the indan part of the molecule and therefore they do not influence the energy

difference between the proposed biologically active conformation of the phenylindans and their globally preferred conformation. But also for the 2,5-dimethylated derivative **26**, the calculations show unambiguously that the changes in affinity (relative to **11**) are not due to conformational energy penalties. In other words, there are no conformational restrictions that exclude the piperazine ring substituted derivatives from interacting with D_1/D_2 receptors in the same biologically active conformation as previously proposed for related compounds.

However, as pointed out above, the structure–activity relationships of the 2,2-dimethylated derivatives are in several ways different from those of their unmethylated counterparts. The apparent high sensitivity toward indan phenyl ring substitution with regard to D_1 affinity observed for the compounds in Table 3 is not seen for the compounds in Table 5. Furthermore, the fact that the compound without the "neuroleptic substituent" in the 6-position, **39**, has potent affinity for both D_1 and D_2 receptors indicates that the unknown, but crucial, interaction of this substituent in previously reported phenylindans with the dopamine receptor sites may be replaced with other stabilizing interactions of the methyl groups with the receptor. Another possibility is that the methyl groups force the molecule into a new binding mode. The greatly increased affinity of the unsubstituted derivative **37** for the D_1 receptor but not for the D_2 receptor might even indicate that a different binding mode is induced only at the D_1 receptor. This could also explain the unexpected high affinity of the 4- and 5-chloro-substituted derivatives **47** and **48** for the D_1 receptor compared with their unmethylated counterparts. We believe that the low affinity of **12** and **13** is due to unfavorable steric interactions, and it is hard to understand why the same is not seen for their methylated analogues, unless a new binding mode is induced.

We have recently proposed a receptor-interaction model for 5-HT_2 antagonists.[36] According to this model piperazinoindans bind to the 5-HT_2 receptor in the same conformation as to the D_2 receptor. However, the model identifies also important differences between the D_2 and the 5-HT_2 pharmacophore regarding tolerance to steric bulk in certain regions of space. For example, substituents in the 5-position of the indan ring system (and the corresponding position of indoles) are not allowed at the D_2 receptor.[22,36] The consistency of this observation in the present series is demonstrated by the loss of D_2 affinity of compound **48**. The 5-HT_2 model identifies also another area of the D_2 pharmacophore sensitive to steric bulk in the vicinity of the indane C2 atom that the compounds in the present series do not interfere with. However the low D_2 affinity and preserved 5-HT_2 affinity (3.3 nM, not shown in Table 4) of compound **25** might indicate another area near the distant piperazine nitrogen atom that is sensitive to steric bulk at the D_2 receptor. Conformational studies and superimposition studies in relation to this hypothesis are in progress.

Experimental Section

Melting points were determined on a Büchi SMP-20 apparatus and are uncorrected. ^{1}H NMR spectra were recorded for all novel compounds at 80 MHz on a Bruker WP 80 DS spectrometer or at 250 MHz on a Bruker AC 250 spectrometer. Where nothing is stated, the spectrum is recorded at 250 MHz. Deuterated chloroform (99.8% D) or dimethyl sulfoxide (99.9% D) were used as solvents. TMS was used as an internal reference standard. Chemical shift values are expressed in ppm values. The following abbreviations are used for multiplicity of NMR signals: br = broad, s = singlet, d = doublet, t = triplet, qui = quintet, h = heptet, dd = double doublet, ddd = double doublet of doublets, dt = double triplet, m = multiplet. Difference NOE spectra and *J*-resolved 2-D spectra were obtained by use of standard Bruker software.

Mass spectra were obtained on a Quattro MS-MS system from VG Biotech, Fisons Instruments. The MS-MS system was connected to an HP 1050 modular HPLC system. A volume of 20–50 μL of the sample (10 μg/mL) dissolved in a mixture of 1% acetic acid in acetonitrile/water 1:1 was introduced via the autosampler at a flow of 30 μL/min into the electrospray source. Spectra were obtained at two standard sets of operating conditions. One set to obtain molecular weight information (MH^+) (21 eV) and the other set to induce fragmentation patterns (70 eV). The background was subtracted. The relative intensities of the ions are obtained from the fragmentation pattern. When no intensity is indicated for the molecular ion (MH^+), this ion was only present under the first set of operating conditions.

The isomeric purity of *trans*-isomers (with respect to *cis*-content) was determined either by TLC or by NMR. TLC determinations were performed 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), by heating the plate for 5 min at 110 °C, and then by 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. In all cases *trans*-isomers had the lowest R_f values.

The most reliable method for estimation of isomeric purity by NMR was to look for the signal from the proton in the 1-position of the indan ring in the *cis*-isomers. While the signals from the two protons in the 1- and 3-position in *trans*-isomers consistently appeared at approximately the same chemical shift, the signal from the proton in the 1-position of *cis*-isomers always appeared at higher field compared to the proton in the 3-position. When a signal was visible, the isomeric purity was estimated by comparing the integral of this signal with 50% of the integral of H_1 and H_3 of the *trans*-isomer.

HPLC analysis was performed on a chromatographic system comprising an AS 2000 autosampler, a L6200 HPLC pump, a T6300 column thermostat, a L4250 UV–vis detector, and a D 6000 computer interface, all from Merck-Hitachi. The system was controlled by an IBM-PC, and data collection and peak integration were performed by the Merck-Hitachi software.

Separation of stereoisomers was performed on the ovomucoid-based ULTRON ES-OVM column (4.6 × 150 mm) from Rockland Technologies. The mobile phase consisted of a mixture of ethanol–2-propanol–tetrahydrofuran–25 mM phosphatebuffer (pH 7.0) 15:5:5:75. The phosphate buffer was prepared in ultrafiltered water and after mixing the mobile phase was degassed by an additional filtration through a 0.45 μm filter. The flow rate on the column was 1.0 mL/min at a temperature of 30 °C. The injection volume of the samples was 25 μL and all chromatograms were recorded at 230 nm.

The 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 if not otherwise stated.

Substituted Piperazines. 2-Methylpiperazine (95%), *trans*-2,5-dimethylpiperazine (98%), and 2,6-dimethylpiperazine (97%, predominantly cis) were purchased from Aldrich. Octahydropyrido[1,2-*a*]pyrazine was prepared as described by Peck and Day.[29]

2,2-Disubstituted or 2,2-spiro-joined piperazines were prepared in the following way.

2,2-Dimethylpiperazine.[37] To a mixture of isobutyraldehyde (790 g, 10.95 mol) and dioxane (39.5 g, 0.45 mol) in dry ether (4 L) was added 11 mL (34 g, 0.21 mol) of bromine at room temperature. The mixture was cooled to 5 °C and further 509 mL (1588 g, 9.93 mol) of bromine was added at 5–10 °C. The reaction mixture was poured into 4 L of ice water whereupon sodium carbonate (600 g) was gradually added with stirring. The organic phase was separated, dried ($MgSO_4$), and distilled to yield 1150 g (69.6%) of 2-bromoisobutyraldehyde, bp 70–77 °C (170 mmHg).

2-Bromoisobutyraldehyde (1070 g, 7.09 mol) was added with vigorous stirring to a mixture of ethylenediamine (2.2 kg, 36.6 mol) and toluene (2 L) at 5–10 °C. The reaction mixture was stirred at room temperature for 1 h and was then refluxed for 30 min. The toluene phase was separated and the lower phase was extracted twice with 500 mL of toluene. The toluene phase was concentrated in vacuo and the residue was distilled to give 450 g (56.6%) of crude 2,2-dimethyl-1,2,5,6-tetrahydropyrazine, bp 80–120 °C (170 mmHg).

To a solution of the crude 2,2-dimethyl-1,2,5,6-tetrahydropyrazine (450 g) in 1 L of ethanol was added 5% Pd/C (20 g) and the reaction mixture was hydrogenated in a Parr apparatus at 3.5 bar until the consumption of hydrogen (2.2 mol) stopped. After filtration the reaction mixture was distilled at atmospheric pressure. The fraction boiling at 140–180 °C was collected and redistilled to yield 159 g (19.8% from 2-bromoisobutyraldehyde) of 2,2-dimethylpiperazine, bp 150–170 °C (760 mmHg). ^{1}H NMR ($CDCl_3$): δ 1.12 (s, 6H), 1.33 (br s, 2H, NH), 2.60 (s, 2H), 2.76 (t, 2H), 2.85 (t, 2H). MS (major signals): *m/z* (%) 115.1 (MH^+, 4),72.1 (10), 57.1 (6), 55.1 (22), 44.2 (21).

The product solidified upon standing (mp below 35 °C).

2,2-Diethylpiperazine, 5,8-diazaspiro[3.5]nonane, 6,9-diazaspiro[4.5]decane, and 1,4-diazaspiro[5.5]undecane were all prepared by a similar procedure.

2,2-Diethylpiperazine: bp 130–140 °C (10 mmHg). ^{1}H NMR ($CDCl_3$): δ 0.80 (t, 6H), 1.31–1.62 (m, 4H), 1.73 (br s, 2H, NH), 2.61 (s, 2H), 2.78 (s, 4H). MS (major signals): *m/z* (%) 143.1 (MH^+, 1), 125.1 (8), 58.1 (7), 55.1 (15), 44.2 (18).

5,8-Diazaspiro[3.5]nonane: kugelrohr distillation, oven temperature 170 °C (760 mmHg), solidifies on standing, mp < 50 °C. ^{1}H NMR ($CDCl_3$): δ 1.52–1.95 (m, 8H), 2.62–2.75 (m, 2H), 2.88–3.00 (m, 2H), 3.05–3.15 (m, 2H). MS (major signals): *m/z* (%) 127.1 (MH^+, 2), 97.0 (9), 84.1 (22), 67.0 (13), 44.1 (16).

6,9-Diazaspiro[4.5]decane: bp 110–115 °C (10 mmHg). ^{1}H NMR ($CDCl_3$): δ 1.45–1.75 (m, 10H), 2.66 (s, 2H), 2.75–2,85 (m, 4H). MS (major signals): *m/z* (%) 141.1 (MH^+, 5), 124.1 (4), 98.1 (9), 81.1 (19), 79.1 (10), 44.2 (16).

1,4-Diazaspiro[5.5]undecane: bp 102–110 °C (10 mmHg) (bp 110 °C, 16 mmHg[38]). ^{1}H NMR ($CDCl_3$): δ 1.40–1.55 (m, 10H), 1.70 (s, 2H, NH), 2.65 (s, 2H), 2.75–2.85 (m, 4H). MS (major signals): *m/z* (%) 155.1 (MH^+, 9), 138.1 (4), 112.1 (6), 95.1 (15), 67.1 (11), 44.2 (10).

General method for preparation of N-unsubstituted and N-methylated compounds.

(±)-*trans*-4-[6-Chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]-2,2-dimethylpiperazine, Hemifumarate (41). A mixture of 1,6-dichloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-indene (28 g, 0.1 mol), 2,2-dimethylpiperazine (15 g, 0.13 mol), and potassium carbonate (30 g) in acetone (250 mL) was refluxed for 18 h. The reaction mixture was evaporated in vacuo and treated with water and ether. The ether phase was separated and extracted with 1 M methanesulfonic acid. The base was liberated with 10 M sodium hydroxide, extracted with ether, and dried ($MgSO_4$). After filtration and evaporation in vacuo the residue was dissolved in acetone and treated with fumaric acid. The fumarate salt was filtered to give 27 g of **41** as the hemifumarate salt, mp 240–241 °C. A sample recrystallized from ethanol had mp 242–244 °C. Isomeric purity (TLC): 95% *trans* isomer. ^{1}H NMR (base in $CDCl_3$): δ 1.16 (s, 6H), 1.79 (br s, 1H) 1.88–2.02 (m, 1H), 2.16 (d, $1H_A$, $NCH_AH_BC(CH_3)_2N$, J_{AB} = 10.7 Hz), 2.22 (d, $1H_B$, J_{AB} = 10.7 Hz), 2.33–2.45 (m, 1H), 2.45–2.58 (m, 1H), 2.59–2.73 (m, 1H) 2.83–3.03 (m, 2H), 4.30–4.43 (m, 2H), 6.89 (d, 1H), 6.93–7.06 (m, 4H), 7.18 (dd, 1H), 7.38 (d, 1H). Anal. ($C_{21}H_{24}ClFN_2 \cdot C_2H_2O_2$) C, H, N.

(±)-*trans*-4-[6-Chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]-1,2,2-trimethylpiperazine, Maleate (28). A mixture of the hemifumarate of **41** (23 g, 0.055 mol), 37% formaldehyde (100 mL), and formic acid (100 mL) was heated on a steam bath for 2 h and was then evaporated in vacuo. The residue was converted to the base in a conventional manner. The base was dissolved in ethyl acetate and treated with maleic acid. The maleate salt was recrystallized from ethyl acetate to give 13.5 g (50%) of **28**·maleate, mp 143–146 °C. Isomeric purity (TLC): >98% *trans*-isomer. ^{1}H NMR (base in $CDCl_3$): δ 1.02 (s, 3H), 1.04 (s, 3H), 1.88–2.01 (m, 1H), 2.17 (d, $1H_A$, $NCH_AH_BC(CH_3)_2N$, J_{AB} = 10.7 Hz), 2.25 (d, $1H_B$, J_{AB} = 10.7 Hz), 2.22 (s, 3H), 2.45–2.75 (m, 5H), 4.31–4.42 (m, 2H), 6.89 (d, 1H), 6.92–7.05 (m, 4H), 7.17 (dd, 1H), 7.37 (d, 1H). Anal. ($C_{22}H_{26}ClFN_2 \cdot C_4H_4O_4$) C, H, N.

(±)-*trans*-9-[6-Chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]-6-methyl-6,9-diazaspiro[4.5]decane, Fumarate (34). ^{1}H NMR (base in $CDCl_3$): δ 1.30–1.72 (m, 8H), 1.83–1.94 (m, 1H), 2.13 (s, 3H), 2.16 (d, $1H_A$, $NCH_AH_BC(CH_3)_2N$, J_{AB} = 10.8 Hz), 2.22 (d, $1H_B$, J_{AB} = 10.8 Hz), 2.38–2.68 (m, 5H), 4.23–4.35 (m, 2H), 6.81 (d, 1H), 6.84–6.98 (m, 4H), 7.09 (dd, 1H), 7.30 (d, 1H). MS (major signals): *m/z* (%) 399 (MH^+), 245 (12), 210 (13), 155 (8), 124 (7), 98 (5), 58 (11). Anal. ($C_{24}H_{28}ClFN_2 \cdot C_4H_4O_4$) C, H, N: calcd, 65.30; found, 64.54.

(±)-*trans*-4-[4-Chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]-1,2,2-trimethylpiperazine, Dioxalate (47). ^{1}H NMR (base in $CDCl_3$): δ 1.03 (s, 3H), 1.04 (s, 3H), 1.88–2.00 (m, 1H), 2.13–2.27 (m, 2H), 2,22 (s, 3H), 2.47–2.70 (m, 5H), 4.48–4.62 (m, 2H), 6.88–6.95 (m, 4H), 7.17–7.35 (m, 3H). MS (major signals): *m/z* (%) 373 (MH^+), 245 (6), 210 (19), 149 (8), 129 (9), 98 (5), 58 (11). Anal. ($C_{22}H_{26}ClFN_2 \cdot C_4H_4O_8$) C, H, N: calcd, 56.47; found, 55.96.

Preparation of N-Alkylated Derivatives (Other Than Methylated). **(±)-*trans*-4-[6-Chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]-2,2-dimethyl-1-(2-propyl)piperazine, Dioxalate (29).** A mixture of **41** (base, 6 g, 0.017 mol), 2-iodopropane (10 g, 0.059 mol) and potassium carbonate (10 g, 0.073 mol) in ethanol (250 mL) was refluxed with stirring for 18 h. The product was worked up as described for **41** above, and 6 g of crude base was obtained. The oxalate salt crystallized from ethyl acetate. The oxalate was recrystallized from methanol/ether to give 3.3 g (33%) of **29**, mp 157–159 °C. Isomeric purity (TLC): 100% *trans*-isomer. ^{1}H NMR (base in $CDCl_3$): 0.89 (s, 3H), 0.92 (s, 3H), 1.00 (s, 6H), 1.77–1.92 (m, 1H), 2.03 (d, $1H_A$, $NCH_AH_BC(CH_3)_2N$, J_{AB} = 10.4 Hz), 2.11 (d, $1H_B$, J_{AB} = 10.4 Hz), 2.28–2.66 (m, 5H), 3.06–3.25 (m, 1H), 4.20–4.32 (m, 2H), 6.80 (d, 1H), 6.83–6.97 (m, 4H), 7.09 (d, 1H), 7.30 (s, 1H). Karl Fischer titration: 2.43% H_2O. Anal. ($C_{24}H_{30}ClFN_2 \cdot C_4H_4O_8$) C, H, N.

(±)-*trans*-4-[6-Chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]-2,2-dimethyl-1-piperazineethanol (30). A mixture of **41** (base, 5.4 g, 0.015 mol), ethyl bromoacetate (3.3 g, 0.020 mol), and potassium carbonate (3 g, 0.021 mol) in methyl isobutyl ketone (200 mL) was refluxed with stirring for 4 h. The reaction mixture was evaporated in vacuo and treated with ether and water. The ether phase was dried ($MgSO_4$) and evaporated to give 7 g of crude ester. The ester was dissolved in dry ether, $LiAlH_4$ (2 g) was added, and the mixture was refluxed for 3 h. The excess $LiAlH_4$ was destroyed with water, the organic phase was decanted, and the product was extracted from the ether phase with 1 N methanesulfonic acid. The base was liberated with 10 N NaOH, extracted with ether, dried, and evaporated in vacuo. The base crystallized from petroleum ether to yield 1.1 g of **30**, mp 79–81 °C. Isomeric purity (TLC): 99% *trans*-isomer.^{1}H NMR ($CDCl_3$): 1.04 (s, 6H), 1.89–2.02 (m, 1H), 2.18 (d, $1H_A$, $NCH_AH_BC(CH_3)_2N$, J_{AB} = 10.7 Hz), 2.25 (d, $1H_B$, J_{AB} = 10.7 Hz), 2.40–2.73 (m, 8H), 3.51 (t, 2H), 4.31–4.42 (m, 2H), 6.90 (d, 1H), 6.93–7.06 (m, 4H), 7.19 (dd, 1H), 7.37 (d, 1H). Anal. ($C_{23}H_{28}ClFN_2O$) C, H, N.

(±)-*trans*-4-[6-Chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]-2,2-dimethyl-1-piperazinepropanol, Dioxalate (31). Methyl malonyl chloride (2 mL, 0.019 mol) was added at room temperature to a mixture of **41** base (1.5 g, 0.004 mol) and triethylamine (5 mL) in methylene chloride (100 mL).

The mixture was stirred at room temperature for 16 h. Water was added, and the organic phase was separated, washed with water, dried, and evaporated in vacuo. The residue was dissolved in ether (200 mL), and lithium aluminium hydride (1 g) was added in portions with stirring. The mixture was refluxed for 3 h and then quenched with water (4 mL). The organic phase was dried and evaporated to give crude **31** as an oil (1.2 g). The product was purified by flash chromatography (silica 40–63 μm, 200 g; mobile phase, ethyl acetate–methanol–triethylamine 80:10:1) to give **31** base as an oil (0.6 g). The dioxalate salt crystallized from ethyl acetate. Yield 0.4 g (16%); mp 100–104 °C. NMR (base in $CDCl_3$): δ 1.07 (s, 3H), 1.09 (s, 3H), 1.55–1.80 (m, 2H), 1.83–1.98 (m, 1H), 2.12–2.30 (m, 2H), 2.38–2.80 (m, 7H), 3.75–3.82 (t, 2H), 4.28–4.41 (m, 2H), 6.88 (d, 1H), 6.92–7.06 (m, 4H),7.18 (dd, 1H), 7.36 (d, 1H). Anal. ($C_{24}H_{30}ClFN_2O \cdot C_4H_4O_8$) C, H, N.

Resolution of Racemic *trans*-Isomers. (+)- and (−)-*trans*-4-[6-Chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]-1,2,2-trimethylpiperazine, Dihydrochloride [(+)-28 and (−)-28]. To a solution of **28** (base, 70 g, 0.187 mol) in 1 L of ethyl acetate was added (+)-*O*,*O*′-dibenzoyl-D-tartaric acid hydrate ((+)-DBT, 70.6 g, 0.189 mol). The clear solution was left at room temperature overnight. The crude (+)-DBT salt was filtered, dried (yield 53 g), and recrystallized from ethyl acetate–methanol. The (+)-DBT salt (mp 123–128 °C) was converted to the base, which was dissolved in acetone and converted to the hydrochloride. Yield 13 g of (−)-**28**, dihydrochloride; mp 201–202 °C; $[\alpha]^{22}_D$ −23.4° (c 0.5, MeOH). ^1H NMR (base in $CDCl_3$): identical to **28** base. Anal. ($C_{22}H_{26}ClFN_2 \cdot 2HCl$) C, H, N.

A previous batch (0.5 g) of lower enantiomeric purity (see Table 2) had mp 202–204 °C and $[\alpha]^{22}_D$ −15.5° (c 1, DMF). Anal. ($C_{22}H_{26}ClFN_2 \cdot 2HCl$) C, H, N. This batch was used for initial screening, as indicated in Tables 4–6.

The first filtrate from the (+)-DBT salt was evaporated in vacuo and converted to the base (38 g), which was dissolved in ethyl acetate and treated with (−)-DBT hydrate (38.3 g) to give the (−)-DBT salt. This salt was converted to the hydrochloride as described for the (−)-enantiomer. Yield 14.8 g of (+)-**28**, dihydrochloride; mp 206–208 °C; $[\alpha]^{22}_D$ +24.5° (c 0.5, MeOH). Anal. ($C_{22}H_{26}ClFN_2 \cdot 2HCl$) C, H, N.

A previous batch (0.5 g) of approximately the same enantiomeric purity (see Table 2) had mp 203–205 °C and $[\alpha]^{22}_D$ +16.5° (c 1, DMF). Anal. ($C_{22}H_{26}ClFN_2 \cdot 2HCl$) C, H, N. This batch was used for the screening, as shown in Table 4.

Compounds **29**, **34**, **35**, **38**, **41** and **54** were separated into their enantiomers using a similar procedure as described above. The physicochemical properties of the enantiomers are shown in Table 2.

(+)- and (−)-*trans*-4-[3-(4-Fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]-1,2,2-trimethylpiperazine, Fumarate [(+)-39 and (−)-39]. To a solution of racemic *trans*-4-[3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]-2,2-dimethylpiperazine (20 g, 0.062 mol, prepared as described above for **41**) in 500 mL of ethyl acetate was added (−)-*O*,*O*′-di-*p*-toluoyl-L-tartaric acid ((−)-DTT, 23.8 g, 0.062 mol). The solution was left at room temperature overnight. The (−)-DTT salt was filtered, dried (yield 15 g), and recrystallized twice from acetone (100 mL) to give 7.5 g of *trans*-4-[3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]-2,2-dimethylpiperazine di-*p*-toluoyl-L-tartrate, mp 163–163.5 °C. The salt was converted to the base, to give 3 g of (−)-*trans*-4-[3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]-2,2-dimethylpiperazine, $[\alpha]^{22}_D$ −6.0° (c 0.5, MeOH).

The first filtrate from the (−)-DTT salt was evaporated in vacuo and converted to the base (8.5 g, 0.026 mol), which was dissolved in ethyl acetate (500 mL) and treated with (+)-DTT monohydrate (10.6 g, 0.026 mol) to give the (+)-DTT salt. This salt was recrystallized once from acetone to give 9.5 g of *trans*-4-[3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]-2,2-dimethylpiperazine di-*p*-toluoyl-D-tartrate, mp 161–162 °C The salt was converted to the base, to give 3.2 g of (+)-*trans*-4-[3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]-2,2-dimethylpiperazine, $[\alpha]^{22}_D$ −6.7° (c 0.5, MeOH).

The two resolved bases were methylated as described above for **28**. Their fumarate salts were crystallized from ethyl acetate, and recrystallized from acetone–methanol. From the (−)-enantiomer was obtained 2.5 g of (−)-**39**, (−)-*trans*-4-[3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]-1,2,2-trimethylpiperazine, monofumarate. Mp 197–199 °C; $[\alpha]^{22}_D$ −2.7° (c 0.5, MeOH). ^1H NMR (base in $CDCl_3$): δ 1.01 (s, 6H), 1.87–2.00 (m, 1H), 2.14–2.27 (m, 2H), 2,21 (s, 3H), 2.47–2.73 (m, 5H), 4.35–4.45 (m, 2H), 6.87–7.07 (m, 5H), 7.15–7.28 (m, 2H), 7.37–7.43 (m, 1H). Anal. ($C_{22}H_{27}FN_2 \cdot C_4H_4O_4$) C, H, N.

From the (+)-enantiomer was obtained 2.5 g of (+)-**39**, (+)-*trans*-4-[3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]-1,2,2-trimethylpiperazine, monofumarate. Mp 198–199 °C; $[\alpha]^{22}_D$ +2.5° (c 0.5, MeOH). Anal. ($C_{22}H_{27}FN_2 \cdot C_4H_4O_4$) C, H, N.

A similar procedure was used for the preparation of the enantiomers of **40** (see Table 2 for physicochemical data).

Pharmacological Test Methods. Animals. Male Wistar rats (Mol:Wist, SPF, 170–270 g) or NMRI mice were used. We have recently described the experimental conditions in detail.[10]

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 Pergolide- or SK&F 38393-Induced Circling Behavior in Rats with Unilateral 6-OHDA-Generated Lesions. This test method is described in detail by Arnt and Hyttel.[39] The experiments were done 2–9 months after lesioning when stable contralatheral circling in response to administration of pergolide (0.05 μmol/kg = 0.02 mg/kg, sc) or SK&F 38393 (4.3 μmol/kg = 1.4 mg/kg, sc) was obtained. Test compounds were injected 2 h before pergolide or SK&F 38393. The effect of individual doses of test drugs is calculated as the 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).

Antagonism of Methyl Phenidate-Induced Gnawing Behavior in Mice. The experiments were performed as described by Pedersen and Christensen.[40] Test compounds were injected ip (or sc) 2 h before methyl phenidate (60 mg/kg), and two mice were placed on corrugated cardboard in each gnawing cage (12 × 25 cm). Five to nine pairs of animals were used per dose. The ability to inhibit methyl phenidate-induced gnawing was evaluated after 1 h by inspection of the corrugated cardboard.

Cataleptogenic Effect in Rats. Catalepsy was measured on a vertical wire grid each hour 1–6 h after test drug administration. Catalepsy was defined as being present after at least 15 s of immobility. The maximum effect between 1 and 6 h after administration is reported. A total of 8–12 animals were used per dose.

Antagonism of Quipazine-Induced Head Twitches. The experimental details are given by Arnt et al.[33] 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 the percentage of the number of head twitches in a quipazine-treated control group.

Receptor Binding. DA D_1 Receptors. Affinity of test compounds for dopamine D_1 receptors was estimated by their ability to displace [^{3}H]SCH 23390 from rat striatal membranes as described by Hyttel.[41]

DA D_2 Receptors. Affinity of test compounds for dopamine D_2 receptors was estimated by their ability to displace [^{3}H]-spiperone from rat striatal membranes as described by Hyttel.[41]

5-HT_{2A} 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.[41]

5-HT_{2C} Receptors. Cell Culture. The affinity for 5-HT_{2C} receptors (formerly called 5-HT_{1C}) was determined by utilizing NIH-3T3 cells transfected with a cloned cDNA encoding the 5-HT_{2C} receptor isolated from a rat choroid plexus library.[42] The 5-HT_{2C} cell line was cultured in DMEM containing 10% selected heat-inactivated dialyzed fetal calf serum, L-glutamine

(2 mM), penicillin (1000 units/mL), and streptomycin (0.1 mg/mL). After 6–7 days in culture the cells were harvested by scraping and centrifuged at 400*g* (1000 rpm) for 5 min, and the resulting cell pellet was frozen at −80 °C for subsequent use in receptor binding assays.

Receptor Binding Assay. Frozen aliquots of 5-HT_{2C} cells were resuspended in binding buffer (50 mM Tris-HCl, pH = 7.7) and homogenized with a Turax homogenizer for 10 s. Aliquots corresponding to 2.5 mg of cell homogenate were incubated with 0.5 nM [^{3}H]mesulergine for 60 min at 37 °C, including various concentrations of test drug for determination of IC_{50} values. Nonspecific binding was determined by including 100 μM serotonin in the binding buffer. The binding was terminated by rapid filtration through printed Filtermate B filters on a 96 well Brandell cell harvester. After filtration the filters were dried for 1 h at 110 °C and a solid scintillation (meltilex 8/HS 14.5 g) was melted into the filters, whereafter the radioactivity was determined in a Beta-plate scientillation counter from Wallac. A specific binding of 88–95% was obtained. The IC_{50} value was estimated from the test of at least five concentrations of test drug. In saturations experiments with [^{3}H]mesulergine an apparent K_D value of 0.43 nM was obtained.

α_1 Adrenoceptors. Affinity of test compounds for α_1 adrenoceptors was estimated by their ability to displace [^{3}H]-prazosin from whole rat brain membranes as described by Skarsfeldt and Hyttel.[43]

Uptake Inhibition in Vitro. Inhibition of DA, NE, and 5-HT uptake in vitro was measured as previously described.[19]

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