Antihypertensive Activity in a Series of 1-Piperazino-3-phenylindans with Potent 5-HT_2-Antagonistic Activity

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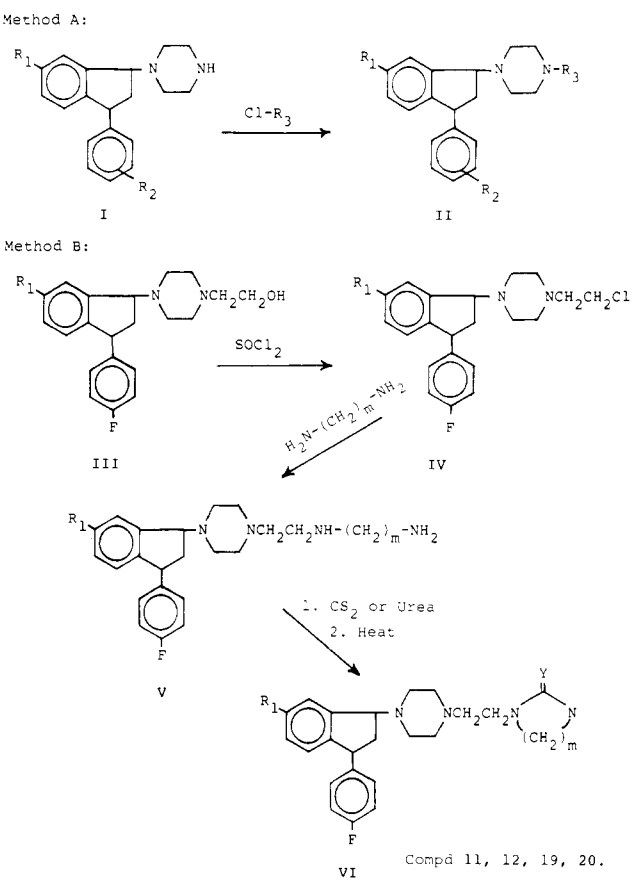
A series of *trans*-1-piperazino-3-phenylindans were synthesized with the goal of replacing their established neuroleptic profile with that of peripheral 5-hydroxytryptamine (5-HT_2) antagonism. Compounds with an unsubstituted or fluoro-substituted 6-position in the indan ring, and which had a five- or six-membered heterocyclic ring attached by an ethylene chain to the piperazine ring, satisfied this objective. Some of the compounds had potent antihypertensive activity in conscious, spontaneously hypertensive rats (SHR). In pithed rats they antagonized the pressor effect induced by 5-HT in doses 100–1000 times lower than doses needed to antagonize the pressor effect of phenylephrine. The effect was stereoselective and associated with enantiomers with 1*R*,3*S* absolute configuration. 1*S*,3*R* enantiomers inhibited the uptake of dopamine and norepinephrine in vitro. The compound with the best antihypertensive activity was (+)-(1*R*,3*S*)-1-[2-[4-[3-(4-fluorophenyl)-1-indanyl]-1-piperazinyl]ethyl]-2-imidazolidinone (Lu 21-098, irindalone). Its pharmacological profile resembled that of the standard compound ketanserin. There was a close structural correspondence between ketanserin and irindalone in a conformation that we recently identified as a D-2 receptor-relevant configuration of its neuroleptic "parent" tefludazine. This suggests that the dopaminergic (D-2) and the serotonergic (5-HT_2) pharmacophores are structurally closely related.

Since the discovery of subclasses of serotonin (5-hydroxytryptamine, 5-HT) receptors[1,2] there has been an increasing interest in developing compounds with selectivity for the different receptor types. By using [^{3}H]spiperone as a ligand for the 5-HT_2 receptor subtype, Peroutka and Snyder[1] demonstrated that compounds belonging to various therapeutical and chemical classes had high affinity for the 5-HT_2 receptor subtype. This was later confirmed by Leysen et al.[3] using tritiated ketanserin (**32**, Figure 1), which behaved as a much more selective 5-HT_2 antagonist[4] than spiperone.

The discovery of **32** made it possible to investigate the pharmacology of a selective 5-HT_2 antagonist.[5] This compound acts preferentially at peripheral 5-HT_2 receptors and has been developed for treatment of cardiovascular diseases. Extensive clinical investigations indicate that **32** is an effective antihypertensive agent.[6] An even more selective compound with a greater central effect has later been developed (**35**, ritanserin).[7] Compound **35** has shown anxiolytic activity in various animal test models and in initial clinical trials it has been reported to show promising effect, especially in patients with "dysthymic disorder".[8,9]

Compounds **32** and **35** have structural elements that clearly can be related to the neuroleptics haloperidol and pimozide, respectively, the side chains now being incorporated in piperidine rings. On the other hand, the quinazolidinedione and thiazolopyrimidinone side chains are new structural elements. In a certain sense, however, these compounds might be considered as evolving from their neuroleptic "parents". Although many neuroleptic compounds (including butyrophenones, thioxanthenes, and phenothiazines) had relatively high affinity for 5-HT_2 receptors,[10] there have been no reports of attempts to develop selective 5-HT_2 antagonists from other neuroleptic structures.

Scheme I



We have previously reported the discovery of a new class of neuroleptic compounds, i.e. the 1-piperazino-3-phenylindans.[11] We found that these compounds, particularly tefludazine (**34**, Figure 2), were also very potent and stereoselective 5-HT_2 antagonists.[12,13] The discovery that the 6-substituent (CF_3 in the case of tefludazine), which is of crucial importance for the neuroleptic activity, is only of minor importance for antiserotonergic activity[13]

(1) Peroutka, S. J.; Snyder, S. H. *Mol. Pharmacol.* **1979**, *16*, 687.
(2) Peroutka, S. J.; Lebovitz, M. R.; Snyder, S. H. *Science (Washington, D.C.)* **1981**, *212*, 827.
(3) Leysen, J. E.; Niemegeers, C. J. E.; Van Nueten, J. M.; Laduron, P. M. *Mol. Pharmacol.* **1982**, *21*, 304.
(4) Leysen, J. E.; Awouters, F.; Kennis, L.; Laduron, P. M.; Vandenberk, J.; Janssen, P. A. J. *Life Sci.* **1981**, *28*, 1015.
(5) Awouters, F. *Drug Dev. Res.* **1985**, *6*, 263.
(6) Symoens, J.; Janssens, M. *Drug Dev. Res.* **1986**, *8*, 159.
(7) Colpaert, F. C.; Meert, T. F.; Niemegeers, C. J. E.; Janssen, P. A. J. *Psychopharmacology* **1985**, *86*, 45.
(8) Meert, T. F. *Drug Dev. Res.* **1986**, *8*, 197.
(9) Reyntjens, A.; Gelders, Y. G.; Hoppenbrouwers, M.-L. J. A.; Bussche, V. G. *Drug Dev. Res.* **1986**, *8*, 205.
(10) Peroutka, S. J.; Snyder, S. H. *Am. J. Psychiatry* **1980**, *137*, 1518.
(11) Bøgesø, K. P. *J. Med. Chem.* **1983**, *26*, 935.
(12) Svendsen, O.; Arnt, J.; Boeck, V.; Bøgesø, K. P.; Christensen, A. V.; Hyttel, J.; Larsen, J.-J. *Drug Dev. Res.* **1986**, *7*, 35.
(13) Bøgesø, K. P.; Hyttel, J.; Christensen, A. V.; Arnt, J.; Liljefors, T. In *Innovative Approaches in Drug Research*; Harms, A. F., Ed.; Elsevier: Amsterdam, 1986; p 371.

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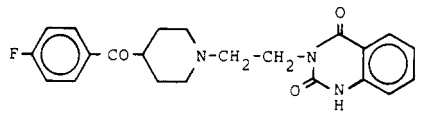

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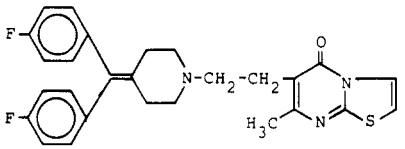
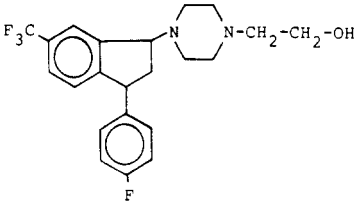


35

Figure 1. The structures of the 5-HT_2 antagonists **32** (ketanserin) and **35** (ritanserin).



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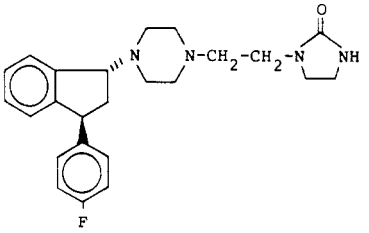


(+) 2

Figure 2. The structures of the neuroleptic compound **34** (tefludazine) and the 5-HT_2 antagonist (+)-**2** (irindalone).

prompted us to attempt developing selective 5-HT_2 antagonists within this chemical class. In this paper we describe the structure–activity relationships (SAR) within a series of these compounds that led to the discovery of irindalone ((+)-**2**, Figure 2), a selective 5-HT_2 antagonist with potent antihypertensive activity.

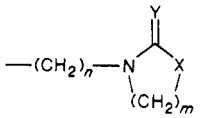
Chemistry

As previously described[11] most of the compounds were obtained by alkylation of the secondary piperazino derivatives I (Scheme I) with the chloro derivatives of the side chains shown in Table I (method A). The starting materials (I) were either purified trans isomers or crude isomeric mixtures (containing approximately 70% trans isomer). In the latter case pure trans isomers of the final products were obtained by recrystallization of the corresponding dimaleate salts.

An alternative method was used for preparation of the imidazolidinethione derivatives **11** and **12** and the pyrimidinone and -thione derivatives **19** and **20** (method B, Scheme I). The piperazinoethanol derivatives III[11] were treated with thionyl chloride to produce the chloroethyl derivatives IV, which were treated with a large excess of ethylene- or propylenediamine to give the derivatives V. Addition of carbon disulfide to a solution of V gave the corresponding dithiocarbamate salts, which on heating in 1-pentanol gave the desired products **11**, **12**, and **20**. Compound **19** was obtained in a corresponding manner from V and urea.

Compound **5** (Table II) was obtained directly from **4** by cleavage of the 4-methoxy group with methionine in methanesulfonic acid.[14]

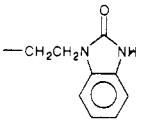
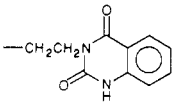
Table I. Structure of Side Chains A–Q (R_3, Table III)



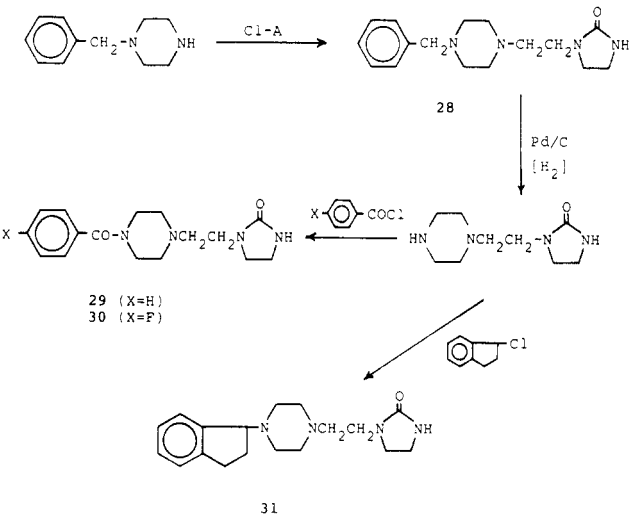
side chain (R_3)

type	n	m	X	Y
A	2	2	NH	O
B	2	2	O	O
C	2	2	CH_2	O
D	2	2	NH	S
E	2	2	N-CH_3	O
F	2	2	N-C_2H_5	O
G	2	2	N-iPr	O
H	3	2	NH	O
I	3	2	O	O
K	2	3	NH	O
L	2	3	NH	S

Miscellaneous Side Chains

type	R_3	type	R_3
M		O	H
		P	CH_3
N		Q	CH_2CH_2OH

Scheme II



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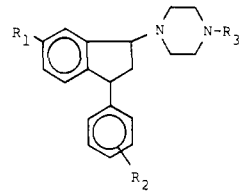
Compound **28** was obtained by alkylation of 1-benzylpiperazine with the chloro derivative of side chain A (see Scheme II). Catalytic debenzylation gave a (piperazinoethyl)imidazolidinone derivative, which was allowed to react with benzoyl chloride or 4-fluorobenzoyl chloride to give **29** and **30**, respectively. Compound **31** was made from the same intermediate by alkylation with 1-chloroindan.

A number of the compounds were resolved by crystallization of their diastereomeric salts with tartaric or dibenzoyltartaric acids (see the Experimental Section). The enantiomeric purity of (+)-**2** and of the enantiomers of **6**, **12**, and **24** were determined by HPLC using a commercially available α-glycoprotein column. Although **7** and **14** are

(14) Nobutaka, F.; Hiroshi, I.; Haruaki, Y. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2288.

Table II. Central Effects and Binding of *trans*-3-Phenyl-1-piperazinoindans[a]



compd	R_1	R_2	R_3[b]	mp, °C	formula[c]	ED_{50}, μmol/kg: methyl phenidate antagonism: mice, ip[d]	ED_{50}, μmol/kg: antagonism of 1-5-HTP head twitches: rats, sc[d]	receptor binding,[e] IC_{50}, nM: [^{3}H]SPI 5-HT$_2$	[^{3}H]SPI D-2	[^{3}H]-PRAZ: α_1
1	H	H	A	169–171	$C_{24}H_{30}N_4O$·dimaleate	>64	26 (17–39)	12[g]	1900	NT[f]
2	H	4-F	A	154–157	$C_{24}H_{29}FN_4O$	>98	1.3 (0.62–2.7)	4.2[g]	930	33
(+)-2	H	4-F	A	89–90	$C_{24}H_{29}FN_4O$	>72	0.56 (0.37–0.84)	3.4[g]	400	26
(−)-2	H	4-F	A	84–86	$C_{24}H_{29}FN_4O$·0.3H_2O	>97	>97	570[g]	13000	540
3	H	4-Cl	A	254–256	$C_{24}H_{29}ClN_4O$·2HCl	>80	40 (16–100)	37[g]	800	NT
4	H	4-OCH_3	A	137–139	$C_{25}H_{32}N_4O_2$	>95	>48	250[g]	15000	1400
5	H	4-OH	A	208–211	$C_{24}H_{30}N_4O_2$·0.4H_2O	>98	>49	310[g]	4000	560
(+)-6	H	2-F	A	151–153	$C_{24}H_{29}FN_4O$·dimaleate	>62	17 (10–29)	NT	NT	NT
(−)-6	H	2-F	A	151–153	$C_{24}H_{29}FN_4O$·dimaleate	>62	>31	NT	NT	NT
7	F	4-F	A	149–151	$C_{24}H_{28}F_2N_4O$	>47	0.13 (0.06–0.27)	6.5	200	24
(+)-7	F	4-F	A	172–174	$C_{24}H_{28}F_2N_4O$·dimaleate	>61	0.096 (0.064–0.14)	4.3	46	10
(−)-7	F	4-F	A	172–174	$C_{24}H_{28}F_2N_4O$·dimaleate	>61	20 (10–40)	320	4500	900
8	H	4-F	B	228–229	$C_{24}H_{28}FN_3O_2$·2HCl	>83	2.7 (0.87–8.4)	130	NT	NT
9	F	4-F	B	220–223	$C_{24}H_{27}F_2N_3O_2$·2HCl·H_2O	18 (11–29)	1.3 (0.76–2.2)	44	NT	NT
10	F	4-F	C	260–263	$C_{25}H_{29}F_2N_3O$·2HCl	18 (11–29)	0.76 (0.38–1.5)	12	85	36
11	H	4-F	D	178–180	$C_{24}H_{29}FN_4S$·dimaleate	>61	0.43 (0.31–0.60)	3.3	NT	NT
12	F	4-F	D	138–142	$C_{24}H_{28}F_2N_4S$	25 (16–40)	0.13 (0.06–0.29)	4.9	NT	NT
(+)-12	F	4-F	D	175–177	$C_{24}H_{28}F_2N_4S$·dimaleate	17 (6.5–44)	0.030 (0.016–0.057)	2.2	29	13
13	H	4-F	E	236–238	$C_{25}H_{31}FN_4O$·2HCl·H_2O	>80	1.4 (0.35–5.6)	13	NT	NT
14	F	4-F	E	239–241	$C_{25}H_{30}F_2N_4O$·2HCl	>78	0.078 (0.041–0.15)	3.3	260	11
(+)-14	F	4-F	E	91–92	$C_{25}H_{30}F_2N_4O$	>91	0.023 (0.012–0.043)	1.0	38	11
(−)-14	F	4-F	E	92–93	$C_{25}H_{30}F_2N_4O$	>91	>45	410	8500	1300
15	F	4-F	F	248–250	$C_{26}H_{32}F_2N_4O$·2HCl	>75	0.092 (0.018–0.45)	4.8	25	34
16	F	4-F	G	250–253	$C_{27}H_{34}F_2N_4O$·2HCl	>73	0.11 (0.047–0.25)	4.8	35	28
17	F	4-F	H	239–242	$C_{25}H_{30}F_2N_4O$·2HCl	55 (21–143)	2.0 (1.0–4.0)	5.6	46	12
18	F	4-F	I	227–230	$C_{25}H_{29}F_2N_3O_2$·2HCl	39 (19–82)	0.31 (0.08–1.2)	22	30	NT
19	F	4-F	K	163–167	$C_{25}H_{30}F_2N_4O$·dimaleate·0.3H_2O	>59	1.2 (0.60–2.4)	11	NT	NT
20	F	4-F	L	187–189	$C_{25}H_{30}F_2N_4S$·dimaleate	23 (5.9–90)	0.11 (0.047–0.25)	7.5	51	NT
21	F	4-F	M	248–251	$C_{28}H_{28}F_2N_4O$·2HCl	>72	0.28 (0.16–0.50)	9.4	25	160
22	H	4-F	N	217–220	$C_{29}H_{29}FN_4O_2$·2HCl	>70	4.4 (1.7–11.4)	3.4[g]	60	5.5
23	F	4-F	N	210–212	$C_{29}H_{28}F_2N_4O_2$·0.1H_2O	>79	2.3 (1.1–4.8)[h]	2.9	19	5.3
24	H	4-F	O	90–91	$C_{19}H_{21}FN_2$	>108	2.5 (1.1–5.8)	30	1900	100
(+)-24	H	4-F	O	154–155	$C_{19}H_{21}FN_2$·dimaleate	>76	1.7 (0.74–3.9)	18	580	37
(−)-24	H	4-F	O	154–155	$C_{19}H_{21}FN_2$·dimaleate	>76	13 (8.7–20)	180	8500	540
25	H	4-F	Q	*i*		>118	0.46 (0.22–0.97)	64	680	62
26	F	4-F	P	*i*		11 (7.3–17)	0.079 (0.03–0.21)	7.7	91	22
(+)-26	F	4-F	P	*i*		2.5 (1.8–3.5)	0.13 (0.059–0.29)	4.9	31	9.3
(−)-26	F	4-F	P	*i*		42 (10–176)	0.49 (0.27–0.88)	43	410	85
27[j]	H	4-F	A	183–185	$C_{24}H_{29}FN_4O$	>98	>196	520[g]	4600	670
32	(ketanserin)					>101	0.79 (0.34–1.8)	1.7	1800	15
33	(prazosin)					>95	0.45[k] (0.16–1.3)	42000	11000	0.36
34	(tefludazine)					0.071 (0.015–0.33)	0.039 (0.21–0.074)	8.4	16	17
35	(ritanserin)					>84	1.2 (0.67–2.2)	4.4	12	47

[a] Isomeric purity: >95% trans. [b] See Table I for definition of R_3. [c] Anal. C, H, N. [d] 95% confidence limits in brackets. [e] All results are the logarithmic mean of at least two determinations each with five concentrations of test compounds in triplicate. [f] NT: not tested. [g] [^{3}H]Ketanserin binding. [h] Compound was given orally. [i] See ref 11. [j] Cis isomer. [k] 33 injected together with citalopram instead of 1.5 h before.

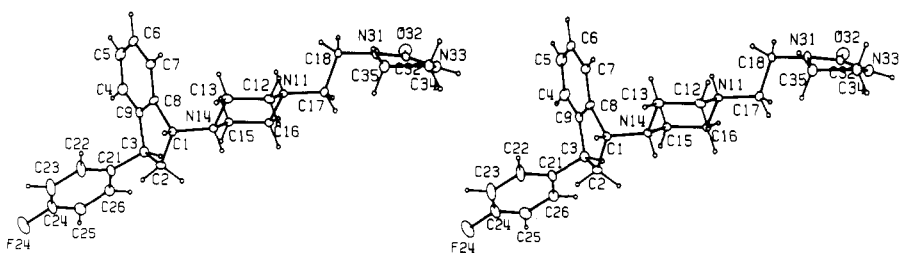


Figure 3. Stereoscopic view of (+)-**2**, L-(+)-tartrate in the crystalline state as established by X-ray analysis.[15]

structurally closely related to the compounds just mentioned, it was impossible to separate the optical isomers of these derivatives on the α-glycoprotein column.

The absolute configuration of (+)-**2** was established as 1*R*,3*S* (see Figure 3) on the basis of single-crystal X-ray analysis of the L-(+)-tartaric acid salt.[15] It was surprising that the absolute configuration of (+)-**2** was 1*R*,3*S* because a previous superimposition study of tefludazine (**34**, Figure 2) and (*S*)-oxyprothepin predicted that the pharmacolog-

(15) Jensen, B. Royal Danish School of Pharmacy, unpublished results.

Table III. Antihypertensive Activity in SHR and Activity in Pithed Rats

compd	% reduction (−) or increase (+) in SHR blood pressure (SAP/DAP) (dose, 5 mg/kg ip)	inhibition (−) or potentiation (+) of the responses of 5-HT or phenylephrine in pithed rats: 5-HT dose: 0.02 mg/kg iv	5-HT ED_{50}, μmol/kg iv	phenylephrine dose: 0.31 mg/kg iv	phenylephrine ED_{50}, μmol/kg iv	phenylephrine ED_{50}/5-HT ED_{50}
(−)-1	−7/−2	−11	ND[a]	0	ND	
2	−33/−43	−68	0.024	−30	3.1	129
(+)-2	−48/−58	−85	0.0045	−42	0.77	171
(−)-2	−3/−11	−11	2.7	+53	ND	
3	−3/−9	+13	ND	+15	ND	
4	−3/−3	−19	ND	+69	ND	
5	−6/−6	−5	ND	+22	ND	
(+)-6	−3/−3	−18	ND	+13	ND	
(−)-6	−8/−8	0	ND	+3	ND	
7	−13/−19	−89	0.017	−27	2.6	153
(+)-7	−24/−31	NT	0.010	−14	1.4	140
(−)-7	+6/+4	+2	0.93	+11	ND	
8	−15/−19	−4	ND	−18	ND	
9	−20/−26	−27	0.084	−19	4.4	52
10	0/−5	−67	ND	−28	ND	
11	−18/−29	−71	ND	−9	ND	
12	−10/−20	−88	0.010	−5	3.7	370
(+)-12	−32/−40	−88	ND	−2	ND	
13	−6/−8	−81	ND	+6	ND	
14	−11/−13	−87	0.010	−12	13	1300
(+)-14	−32/−42	−89	0.0043	−29	2.2	550
(−)-14	+1/−1	−6	ND	+72	ND	
15	+4/+4	−94	ND	−9	ND	
16	−5/0	−79	ND	−5	ND	
17	−12/−19	−68	0.031	−28	2.7	87
18	−12/−18	−32	ND	−7	ND	
19	0/0	−60	ND	−1	ND	
20	−13/−19	−67	ND	−7	ND	
21	−15/−11	−52	ND	−21	ND	
22	−22/−27	−35	0.10	−42	0.77	7.7
23	−29/−46	−52	0.032	−57	0.43	13
24	−10/−13	−13	ND	+7	ND	
+)-24	−25/−31	−40	0.10	+10	8.3	83
(−)-24	−2/−7	−3	ND	+41	ND	
25	−27/−31	−15	0.33	−12	3.4	10
26	−15/−16	−85	ND	−19	ND	
(+)-26	−28/−28	−79	ND	−48	ND	
(−)-26	−5/−6	−43	ND	+5	ND	
27	−3/−2	−3		+33		
32	−32/−37	−62	0.024	−14	3.2	133
33	−32/−39	0	>12	−100	0.0095	<0.0008
34	−18/−24	−78	0.035	−27	2.4	69
35	+10/+9	−95	ND	+16	ND	

[a] ND = not determined.

ically active configuration of the phenylindan dopamine (DA)/5-HT antagonists should be 1*S*,3*R*.[11] Therefore we investigated the configuration of a series of pharmacologically interesting phenylindan derivatives by use of CD spectra[16] and found that the configuration of the more active enantiomer of DA/5-HT antagonists (including the active enantiomers of **34**) was invariably 1*R*,3*S*.[13] We also found that piperazinoindan derivatives with potential antidepressant activity (DA-/norepinephrine (NE)-uptake inhibitors)[11,13] had the 1*S*,3*R* configuration. An extensive molecular modelling study of (1*R*,3*S*)-**34** and (*S*)-octoclothepin has later given a plausible explanation for the discrepancy between the original prediction of the absolute configuration of phenylindan antagonists and the experimental results obtained with (+)-**2**.[17]

Methods and Results

As the new compounds were derived from closely related derivatives with neuroleptic activity[11] it was essential to measure affinity for dopamine (DA) receptors. This was done by measuring their ability to inhibit [^{3}H]spiperone binding to rat striatal membranes. In vivo DA-antagonistic activity was measured by antagonism of methyl phenidate induced gnawing stereotypies in mice.

Affinity for brain 5-HT_2 receptors was measured by inhibition of the binding of either [^{3}H]spiperone or [^{3}H]ketanserin to rat cortical membranes. In vivo central 5-HT_2-antagonistic activity was assessed by the ability of the compounds to antagonize quipazine- or L-5-hydroxytryptophan (L-5-HTP) plus citalopram-induced head twitches in rats. Affinity for α_1 receptors was measured by inhibition of [^{3}H]prazosin binding to rat cerebral membranes. The results of these experiments are shown in Table II and for the compounds **28–31** in Table IV.

The antihypertensive effect of the compounds was measured as the reduction of systolic and diastolic arterial blood pressure (SAP/DAP, Table III) in conscious, spontaneously hypertensive rats (SHR). All compounds were tested in a standard dose of 5 mg/kg, ip. The results in the table, therefore, cannot be compared strictly quantitatively, but should rather be considered as a qualitative indication of the effect. This proved to be satisfactory for screening purposes, but for detailed evaluation of the antihypertensive effect we had to construct a dose–re-

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Table IV. Pharmacological Effects and Binding of Compound 28–31[a]

compd	ED$_{50}$,[b] μmol/kg sc: methyl phenidate antagonism, mice	ED$_{50}$,[b] μmol/kg sc: antagonism of quipazine head twitches, rats	% changes in SHR blood pressure (SAP/DAP) (dose 5 mg/kg ip)	receptor binding: IC$_{50}$,[c] nM: [^{3}H]KET 5-HT$_2$	[^{3}H]SPI D-2	[^{3}H]PRAZ α_1
28	>139[d]	>4.3[e]	+15/+33	>1000	>1000	>10000
29	>132	>8.3	+6/+6	4800	>1000	NT
30	>125	1.8 (0.8–4.1)	+11/+10	58000	>1000	NT
31	>127	>8.0	+5/+6	5100	62000	NT

[a] See the Experimental Section for physical–chemical data. [b,c] See footnote *d* and *e* in Table II. [d] The compound was given ip. [e] Antagonism of L-5-HTP head twitches.

Table V. Uptake Inhibition of Selected Compounds

compd	inhibn of [^{3}H]amine uptake (rat brain synaptosomes): IC$_{50}$,[a] nM: NE	DA	5-HT
(+)-**2**	22000	25000	14000
(−)-**2**	69	140	9700
(+)-**7**	2500	5700	720
(−)-**7**	17	67	2200
(+)-**24**	450	280	42
(−)-**24**	140	220	400
(+)-**26**	12000	1700	3900
(−)-**26**	28	81	610
(±)-**27**	44	100	>100000

[a] See footnote *d* in Table II.

sponse curve in order to estimate ED$_{10}$ values for the most active compounds (not shown in Table III). Furthermore, the peripheral blockade of the 5-HT-induced pressor effect in adrenalectomized pithed rats was measured and compared to the corresponding blockade of phenylephrine-induced pressor responses in pithed rats. For compounds with estimated ED$_{50}$ values, the ratio between phenylephrine antagonism and 5-HT antagonism was calculated as a measure of peripheral 5-HT/α_1 selectivity. These results are shown in Tables III and IV.

Finally, we have previously reported that cis isomers and 1*S*,3*R* enantiomers of a number of 1-piperazino-3-phenylindans are potent inhibitors of DA and NE uptake.[11,13] Some of the enantiomeric pairs and the cis isomer **27** of **2** were therefore checked for uptake-inhibiting properties (Table V).

The compounds reported here were either unsubstituted or fluoro substituted in the 6-position of the indan ring system. As previously reported, neuroleptic activity depended on proper substitution in this position. This is exemplified by the high potency of **34** in the methyl phenidate test in contrast to the inactivity of the corresponding unsubstituted derivative **25** (Table II). However, compound **25** still had considerable affinity for 5-HT$_2$ receptors and in vivo was an effective 5-HT antagonist both in the head twitch model and in the pithed rat, indicating that 5-HT$_2$-antagonistic activity was less sensitive to substitution in the 6-position. We also found that the relatively potent neuroleptic activity found in some 6-fluoro-substituted derivatives, such as **26** and (+)-**26**,[11,13] was abolished in the 1-ethyl-2-imidazolidinone-substituted derivative **7**. Furthermore, it was interesting that while **7** was equipotent with **34** as a 5-HT antagonist in the pithed rat, it was weaker in the test for central 5-HT$_2$-antagonistic activity. In the SHR it showed an effect similar to that of **32**.

The unsubstituted analogue of **7**, compound **2**, had an even better profile than **7**. It had very low affinity for central DA receptors and lower central 5-HT$_2$-antagonistic activity while it was more potent in the SHR. In the pithed rat the compound displayed a similar potency and selectivity.

The compound without 4′-fluoro substitution, **1**, was almost inactive in all test models. Other substituents in the 3-phenyl ring, such as 4′-chloro, 4′-methoxy, 4′-hydroxy, and 2′-fluoro (compounds **3**, **4**, **5**, and (+)-**6**) also gave essentially inactive compounds. This indicated that the 4′-position in this series was just as sensitive to changes of the 4′-fluoro substitution as previously described for the neuroleptic compounds.[11] Therefore, further work focused on structural variations of the 2-imidazolidinone ring of **2** and **7**.

Before going further into these SAR it should be explained that investigation of the activity of stereoisomers confirmed our earlier findings[11,13] in this area. The cis isomer of **2**, i.e. **27**, had no effect in the head-twitch model and no antihypertensive activity in accordance with its very weak affinity for postsynaptic receptor sites. We found, however, that like other *cis*-1-piperazino-3-phenylindans, **27** inhibited both DA and NE uptake in vitro (Table V). Likewise, as previously described for **26**, the (−) enantiomers of **2** and **7** inhibited both DA and NE uptake (Table V). These enantiomers had no antihypertensive activity, but in the pithed rat (−)-**2** and (−)-**7** potentiated the phenylephrine response, perhaps because of the NE-uptake-inhibiting activity of these compounds.

The (+) enantiomers of **2** and **7** had potent antihypertensive activity in the SHR. The ED$_{10}$ values (ip) in SAP/DAP were 0.70/0.51 and 1.5/1.0 μmol/kg for (+)-**2** and (+)-**7**, respectively. By comparison the ED$_{10}$ values for compound **32** were 1.6/1.2 μmol/kg. In the pithed rat (+)-**2** and (+)-**7** were extremely potent antagonists of the 5-HT-induced pressor effect with a selectivity ratio between 5-HT and phenylephrine antagonism of 171 and 140 for (+)-**2** and (+)-**7**, respectively. On account of greater peripheral selectivity and a weaker central effect of (+)-**2**, this compound was considered to have the best profile so far.

Because of the relatively potent NE- and DA-uptake-inhibiting properties of the (−) enantiomers, it became obvious that only a pure enantiomer, and not a racemate, could be selected for further development in this series. Obviously, the measurements obtained for racemates would have to be treated with a certain caution. However, as the DA- and NE-uptake inhibition of the (−) enantiomers did not influence the response in the head-twitch model, and only to a certain degree influenced the response in the SHR and the pithed rat, it nevertheless seemed reasonable to use the effects of racemates in the evaluation of SAR.

The 2-imidazolidinone ring of **2** and **7** was modified in various ways. The 3-methyl derivative of **2**, compound **13**, was very weak in the SHR, although its profile otherwise seemed close to that of **2**. The 3-methyl derivative of **7**, i.e. **14**, and the corresponding (+) enantiomer, (+)-**14**, proved to be the most potent compounds in the head-twitch model. In the pithed rat these compounds had the highest selectivity ratio. However, because of the greater central effect and the weaker effect in the SHR, the overall

profile of (+)-14 was no better than that of (+)-2. Also, (−)-14 potentiated the phenylephrine response, possibly because of NE-uptake inhibition. The 3-ethyl derivative, 15, and the 3-isopropyl derivative, 16, were also potent 5-HT antagonists in the head-twitch model and in the pithed rat, but they were inactive in the SHR.

The propylene side chain derivative of 7, compound 17, had similar activity in the SHR, but had greater affinity for D-2 receptors in accordance with a weak effect in the methyl phenidate test. Expansion of the imidazolidinone ring in 7 to the corresponding six-membered pyrimidinone ring gave a derivative, 19, that was inactive in the SHR and rather weak in the head-twitch model. The 2-thione derivatives of 7 and 19 (12, (+)-12, and 20) were all active in the SHR, but in addition they had an undesired neuroleptic activity. The 2-thione derivative of 2, compound 11, had no neuroleptic activity, but was slightly more active than 2 in the head-twitch model and had weaker effect in the SHR. The benzimidazolidinone derivative 21 had greater affinity for D-2 receptors than 7 and was apparently less selective in the pithed rat. The two quinazolinedione derivatives 22 and 23 (in which the side chain of 32 was combined with the structure of 2 and 7) were less selective in vitro and far less selective 5-HT antagonists in the pithed rat, but both had good effect in the SHR.

Introduction of an oxazolidinone ring instead of the imidazolidinone ring in 2 and 7 gave compounds 8 and 9, which apparently were weaker and less selective 5-HT antagonists. In addition, some neuroleptic activity reappeared in 9 The same tendency was seen in 18, which was the oxazolidinone derivative of 17. The neuroleptic activity also reappeared in the pyrrolidinone derivative 10, while the antihypertensive activity disappeared.

Removal of the 4′-fluorphenyl ring of 2 gave a compound 31 (Table IV) with more than 200 times lower affinity for 5-HT_2 receptors and no activity in vivo. The related derivatives 28–30 were inactive with the exception of 30, which had a moderate 5-HT_2-unrelated effect in the test for quipazine antagonism.

The study of the metabolism of 34[18] showed that the secondary piperazine derivative was a major metabolite of this compound. This suggested that we should investigate the effects of the secondary amine 24 and its corresponding enantiomers. The potential metabolite of (+)-2, i.e. (+)-24, retained efficacy in the SHR, but was a less selective 5-HT antagonist (compared to α_1 antagonism) in the pithed rat and in the binding assays. In vitro it inhibited the 5-HT uptake (Table V), which effect seemed not to have any functional correlate as the compound could not potentiate 5-HTP in mice.[18] Preliminary investigations have shown that (+)-24 is a metabolite of (+)-2 in the rat, but probably not a major one.

Compound (+)-2 (Lu 21-098, irindalone) was selected for further pharmacological and toxicological characterization. The detailed in vivo[19] and in vitro[20] pharmacology, and the cardiovascular profile of this compound, will be published elsewhere. Clinical trials with (+)-2 for treatment of hypertension are in progress at this moment.

Discussion

When the work with the present series of compounds started, the goal was to develop a peripherally acting 5-HT_2 antagonist from centrally active compounds that we knew were potent antagonists of DA, 5-HT_2, and α_1 receptors. Although DA antagonism was a clearly undesirable effect, it was not then clear what role the α_1-antagonistic effect of 32 played in its antihypertensive effect. It was therefore an interesting perspective to develop a compound with a higher 5-HT_2/α_1 receptor selectivity than 32 in order to clarify this controversial issue.

As already discussed above, it was relatively simple to obtain compounds without neuroleptic activity while retaining 5-HT_2-antagonistic activity. A high correlation has been found between head-twitch antagonism and 5-HT_2 receptor binding[21,22] and methyl phenidate antagonism and D-2 receptor binding,[23] respectively. Inspection of Table II, however, showed that a high selectivity in vivo was not accompanied by a similar selectivity in the binding assays. The compounds were also without neuroleptic activity in rats (antagonism of amphetamine- or apomorphine-induced stereotypies[18]). The in vivo ratio between DA and 5-HT_2 antagonism was, for example >635 and >4000 for (+)-7 and (+)-14, respectively, while the ratios in vitro were 11 and 39. One explanation could be that the head-twitch model was much more sensitive than the antistereotypy model. However, comparison of compounds (+)-7 and (+)-26 showed that while they had the same profile in vitro and were equipotent in the head-twitch model, they had very different neuroleptic activity. 35 also carried high D-2 affinity in vitro but had no neuroleptic activity. This paradox has been explained by the large difference in drug–receptor dissociation half-times for 35 at 5-HT_2 receptors (160 min) and D-2 receptors (11 min), respectively.[24] Perhaps the different in vivo/in vitro selectivities observed in our series of compounds can be explained similarly. Many of the compounds had long-lasting effects in the head-twitch model (from about 24 h for (+)-2[19] to several days for (+)-7 and (+)-14[18]), indicating perhaps a long dissociation time from 5-HT_2 receptors.

The pithed rat model (Table III) was used to evaluate peripheral 5-HT_2/α_1 selectivity. Also in this model the selectivity ratios differed from the in vitro selectivity ratios. As already mentioned, it was of interest to find a compound with a higher peripheral 5-HT_2/α_1 receptor selectivity than 32 so as to see what role the α_1-receptor antagonism played in its antihypertensive effect. However, during the work with the present series of compounds, it was reported in the literature that highly selective 5-HT_2 receptor antagonists such as 1-(1-naphthyl)piperazine[25] and the ergoline derivative LY 53857[26] did not lower the blood pressure in the SHR.

As mentioned, the ED_{10} values for reduction of SAP/DAP in the SHR were about 1 μmol/kg for (+)-2, (+)-7, and 32. These doses were much closer to the ED_{50} values for antagonism of the phenylephrine pressor response than to the ED_{50} values for 5-HT antagonism (Table III). Compounds such as 15, 16, and 19, which did not lower the blood pressure in the SHR in a dose of 5 mg/kg, ip,

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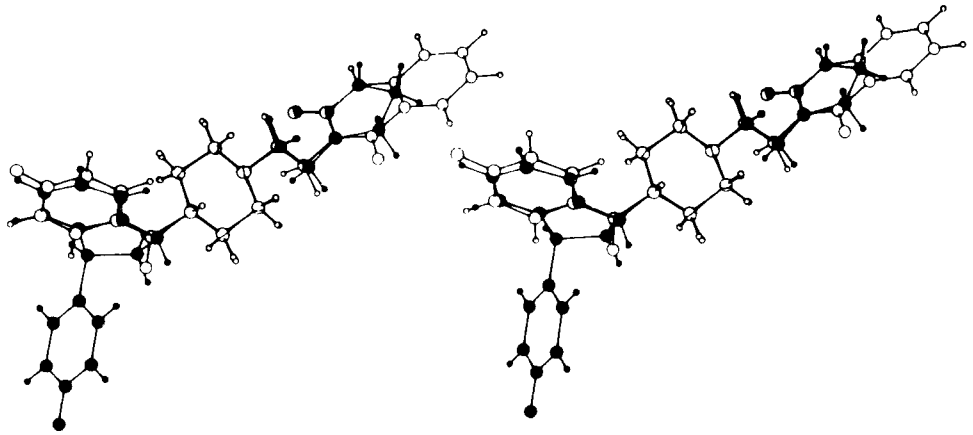

Figure 4. Least-squares superimposition of (+)-**2** (black atoms, except the piperazine ring) and **32** (white atoms). Included in the fitting procedure were (1) NCON fragments, (2) piperazine–piperidine heavy atoms, (3) C-1 (in indan) and carbonyl carbon in **32**. Mean distance between fitted atoms is 0.063 Å.

did not inhibit the phenylephrine-induced pressor response in the pithed rat in a dose of 0.31 mg/kg, iv. On the other hand, the acute hemodynamic profile of the indan derivatives[18] and **32**[27] was clearly different from that of selective α_1-receptor antagonists such as prazosin (**33**). Furthermore, it has been shown that pretreatment of SHR with **35** (which in itself had no antihypertensive activity; also see Table III) potentiated the hypotension induced by administration of a threshold dose of prazosin (**33**).[28] This experiment indicates a synergism between the 5-HT$_2$-antagonistic effect of **35** and the α_1-antagonistic effect of **33**. In compounds like **32** and (+)-**2** such a "synergism" is apparently "built-in" because some α_1-antagonistic activity is retained in addition to their strong 5-HT$_2$-antagonistic activity. This "built-in" synergism parallels the effect of these compounds on the 5-HT- and NE-induced contractions in the rabbit small mesenteric artery. Compound (+)-**2** inhibited both 5-HT- and NE-induced contractions (but had a 22 times more potent effect on the 5-HT-induced contractions; IC_{50} = 3.7 nM). Combination of 5-HT and NE caused contractions 5–10 times higher than the sum of the contractions induced by 5-HT or NE alone. It was shown that (+)-**2** inhibited both this contraction and the 5-HT-induced potentiation of the NE response. Compound **32** had a similar profile, but was less selective and less potent.[20]

An international working group has concluded that the therapeutic effect of **32** in essential hypertension in humans cannot be explained adequately by either peripheral α_1- or 5-HT$_2$-receptor antagonism alone.[29] In principle, it is desirable to keep the α_1 antagonism as low as possible in order to minimize side effects such as orthostatic hypotension, and in this respect, (+)-**2** has peripheral 5-HT$_2$/α_1 selectivity that is comparable to that of **32** (or even slightly better).

Since the pharmacological profiles of (+)-**2** and **32** are so similar, a comparison of their three-dimensional structures was of interest. However, this raised the question of finding relevant conformations of the compounds for a superimposition study. It would have been helpful to have a model of a hypothetical 5-HT$_2$ receptor site, but there was no such model available. On the contrary, Leysen and Tollenaere pointed out that the SAR of 5-HT$_2$ receptor binding was complex due to a wide variety of structurally divergent antagonists.[21] In short, a suitable approach for 5-HT$_2$ receptor modelling was lacking. The problem of 5-HT$_2$ receptor modelling seems on the other hand not to be so different from the problem of DA receptor modelling. Despite the variety of apparently structurally unrelated DA antagonists, several models for the DA receptor have been suggested in the last ten years.[17,30–32]

Many DA antagonists have a complex profile and are also potent antagonists of the 5-HT$_2$ receptor[10,13,24] and other receptors. Key compounds in DA receptor models are (+)-butaclamol and (+)-dexclamol, which, because of their rigid structure and high stereoselectivity, have been extensively used as templates of the DA receptor. However, (+)-butaclamol displays an equally high affinity and stereoselectivity for 5-HT$_2$ receptors.[13] An obvious approach to developing a 5-HT$_2$ receptor model would therefore be to fit selective 5-HT$_2$ antagonists into existing DA receptor models and identify structural differences between selective and nonselective compounds.

In this respect (+)-**2** can be regarded as a key compound. We have recently reported a DA receptor model based upon receptor-relevant conformations of **34** and (*S*)-(+)-octoclothepin.[17] (+)-Dexclamol can also fit nicely into this model. These three compounds are very potent 5-HT$_2$ antagonists, too. Because of the structural similarity of **34** and (+)-**2**, the latter compound can easily fit into this model.

In Figure 4 compound **32** has been superimposed on (+)-**2** by matching structurally corresponding parts (see caption to Figure 4). In the superimposition study, the conformation of (+)-**2** is identical with that of the DA receptor relevant conformation of **34**.[17] Molecular mechanics calculation (MMPMI) showed that the steric energy of this conformation was 0.6 kcal/mol above the energy of the crystalline state,[15] and that the energies of the X-ray conformation of **32**[33] and the conformation used in

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the superimposition study were essentially the same.

Tollenaere et al. suggested on the basis of a conformational analysis of **32** that its receptor-relevant conformation should strongly resemble the X-ray conformation.[34] However, this analysis concentrated on the conformation of the ethylene bridge connecting the piperidine ring and the quinazolinedione ring system. The receptor-relevant conformation of **32** that we suggest here only differs from the X-ray structure with regard to the *p*-fluorophenyl ring (the benzoyl moiety is rotated 117°). The conformation of this part of the molecule has been discussed separately by Tollenaere et al.[35] They found that the benzoyl moiety is conformationally flexible over a broad subspace, which also includes the receptor relevant conformation we suggest. Therefore, our analysis of a receptor-relevant conformation of **32** confirms Tollenaere's conclusion about the ethylene bridge conformation and supplements their analysis of the position of the 4-fluorophenyl ring.

Figure 4 shows immediately that the superimposition of (+)-**2** and **32** results in an exceedingly good fit. However, it is also obvious that the 4-fluorophenyl ring in (+)-**2** is a missing structural element in **32**. The inactivity of **31** (Table IV) shows that this ring is essential to the activity of (+)-**2**. Replacement of the indan ring part of **31** with groups more similar to the 4-fluorobenzoyl part of **32** (compounds **28–30**) also results in inactive compounds.

Compound **35** (Figure 1) has a very long dissociation half-time[24] (160 min) from the 5-HT_2 receptor site whereas compound **32** has a much shorter half-time of only 5.8 min.[24] In addition, (+)-**2** and related derivatives have a longer duration of action in the head-twitch model than **32**. Our hypothesis is that the longer duration of action of **35** and the indan derivatives may be associated with increased binding ability to the 5-HT_2 receptor because the extra 4-fluorophenyl rings bind to an additional site.

Whether the superimposition study in Figure 4 is a valid model of the serotonergic (5-HT_2) pharmacophore must of course be tested by fitting other 5-HT_2 antagonists into the model. As the model assumes great similarity between the dopaminergic and the serotonergic pharmacophores, it is also important to explain why some DA antagonists (such as the benzamides) have no 5-HT_2 receptor affinity.

The SAR of the piperazinoindans reveal an important difference between the DA and the 5-HT_2 receptor sites: While substitution in the 6-position is necessary for DA-antagonistic activity, the present series demonstrates that such substitution is not necessary for 5-HT_2-antagonistic activity.

Because the 6-CF_3 group in **34** and the 8-chloro atom in (*S*)-(+)-octoclothepin were neatly superimposed in the DA receptor model mentioned above,[17] it would be interesting to investigate whether unsubstituted thiepins have any 5-HT_2-antagonistic activity. Phenothiazines and thioxanthenes without their "neuroleptic" 2-substituents might also be selective 5-HT_2 antagonists. Further work is in progress at the moment in order to define more precisely similarities and differences between the dopaminergic and the serotonergic pharmacophores.

Experimental Section

Melting points (uncorrected) were determined on a Büchi SMP-20 apparatus. ^1H NMR spectra were recorded at 80 MHz and ^{13}C NMR spectra were recorded at 20 MHz on a Brucker WP 80 DS spectrometer. Me_4Si was used as internal reference standard. All compounds were routinely checked by TLC and ^1H NMR. NMR data were consistent with the indicated structures. The isomeric purity of the cis and trans isomers 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 complete 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 opposite isomer or small samples of the substance itself. Trans isomers had in all cases the lowest R_f values. Microanalyses (within ±0.4% of theoretical values except where noted) were performed by Lundbeck Analytical Department. Some of the salts retained a partial mole of H_2O despite drying in vacuo. This was confirmed by Karl Fischer (KF) determination.

Preparation of Heterocyclic Chloroalkyl Side Chains. 1-(2-Chloroethyl)-2-imidazolidinone[36] and 1-(3-chloropropyl)-2-imidazolidinone were prepared by treating the corresponding hydroxyalkyl derivatives[37] with thionyl chloride. Literature methods were used for preparation of 3-(2-chloroethyl)-2-oxazolidinone and 3-(3-chloropropyl)-2-oxazolidinone,[38] 3-methyl-, 3-ethyl-, and 3-isopropyl-1-(2-chloroethyl)-2-imidazolidinone,[39] 1-(2-chloroethyl)-benzimidazolin-2-one,[40] and 3-(2-chloroethyl)-2,4(1*H*,3*H*)-quinazolinedione.[41]

***trans*-1-[3-(4-Fluorophenyl)indan-1-yl]piperazine (24).** A mixture of 1-chloro-3-(4-fluorophenyl)indan[11] (61 g, 0.25 mol), piperazine (100 g, 1.16 mol), and potassium iodide (2 g) in methyl isobutyl ketone (400 mL) was refluxed with stirring for 3 h. The mixture was cooled, water was added, and the organic phase was separated and evaporated in vacuo. The residue was dissolved in ether and extracted with a 2 N solution of methanesulfonic acid in water. This extract was basified with concentrated ammonium hydroxide and extracted with ether. After the extract was dried ($MgSO_4$) and evaporated in vacuo 63 g (85%) of an isomeric mixture of **24** and the corresponding cis isomer was obtained. Conversion of the isomeric mixture to the dimaleate salt and recrystallization from ethanol gave the dimaleate of the trans isomer. From this salt was obtained 54 g (73%) of **24** as a crystalline base, mp 89–90 °C. Some of the base was dissolved in acetone and acidified with a saturated solution of HCl in ether. The dihydrochloride salt was recrystallized from ethanol–ether to give **24**·2HCl, mp 233–236 °C; isomeric purity >95% trans isomer (TLC). Anal. ($C_{19}H_{23}Cl_2FN_2$) C, H, N.

Method A. General Remarks. Starting materials for compounds prepared by method A were used as either purified trans isomers (**24** or the corresponding 6-fluoro derivative) or crude isomeric mixtures containing 20–30% of the cis isomer. In the latter case the trans isomers in most cases were purified as described above for **24** via their dimaleate or dioxalate salts.

Method A. Example. *trans*-1-[2-[4-[3-(4-Fluorophenyl)-1-indanyl]-1-piperazinyl]ethyl]-2-imidazolidinone (2). A mixture of **24** (54 g, 0.18 mol), 1-(2-chloroethyl)-2-imidazolidinone (29 g, 0.20 mol), potassium carbonate (30 g, 0.21 mol), and potassium iodide (2 g) in methyl isobutyl ketone (300 mL) was refluxed with stirring for 16 h. The reaction mixture was worked up as described above for **24** to yield 76 g of crude product. This oil was dissolved in ethyl acetate–isopropyl ether and seeded with a crystal of pure **2**. After crystallization overnight in a refrigerator (at 5 °C) there was obtained 37 g (48%) of pure

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2, mp 154–157 °C, isomeric purity >95% trans isomer (TLC). Anal. ($C_{24}H_{29}FN_4O$) C, H, N.

The corresponding cis isomer, **27**, was obtained in a similar way from the cis isomer of **24** obtained from the filtrate of the above-mentioned dimaleate salt of **24**, mp 183–185 °C, isomeric purity >99% cis isomer (TLC). Anal. ($C_{24}H_{29}FN_4O$) C, H, N.

Method B. Example 1. *trans*-1-[2-[4-[3-(4-Fluorophenyl)-6-fluoro-1-indanyl]-1-piperazinyl]ethyl]-2-imidazolidinethione (12). A mixture of *trans*-4-[3-(4-fluorophenyl)-6-fluoro-1-indanyl]-1-piperazineethanol (40 g, 0.11 mol), thionyl chloride (15 mL), and DMF (0.7 mL) in chloroform was refluxed for 1 h. The mixture was cooled, and the crystals were filtered and washed with ethyl acetate and ether to give 45 g of *trans*-1-(2-chloroethyl)-4-[3-(4-fluorophenyl)-6-fluoro-1-indanyl]piperazine hydrochloride, mp 250–255 °C. Twenty grams (0.048 mol) of this hydrochloride was added to a solution of ethylenediamine (50 g) in ethanol (200 mL), and the resulting mixture was refluxed for 2 h. The reaction mixture was evaporated in vacuo and treated with water and methylene chloride. The organic phase was washed with water and dried ($MgSO_4$) to yield 19 g (99%) of crude *trans*-1-[2-[(2-aminoethyl)amino]ethyl]-4-[3-(4-fluorophenyl)-6-fluoro-1-indanyl]piperazine. A sample was converted to the maleate salt, which was recrystallized from methanol to give the pure tetramaleate salt, mp 158–162 °C. Anal. ($C_{39}H_{46}F_2N_4O_{16}$) C, H, N.

Carbon disulfide (5 mL) was added to a solution of the crude diamine base (19 g) in ethanol (100 mL) and methylene chloride (100 mL) whereupon the reaction was kept at room temperature for 2 h. The oily dithiocarbamate salt crystallized after evaporation of the solvents in vacuo, mp 70 °C.

A slurry of the salt in 1-pentanol (200 mL) was refluxed for 1 h; hydrogen sulfide evolution started at ca. 100 °C. The solvent was evaporated in vacuo and the residue was dissolved in ether and purified as described above by extraction with 2 N methanesulfonic acid followed by liberation and extraction of the base to yield 18 g of crude **12**, which crystallized from methanol–isopropyl ether. After recrystallization from methylene chloride–isopropyl ether there was obtained 11 g of **12**, mp 138–142 °C. Anal. ($C_{24}H_{28}F_2N_4S$) C, H, N.

Method B. Example 2. *trans*-1-[2-[4-[3-(4-Fluorophenyl)-6-fluoro-1-indanyl]-1-piperazinyl]ethyl]-2(1*H*)-pyrimidinone (19). A mixture of the chloroethyl derivative described in example 1 (45 g 0.11 mol) and 1,3-diaminopropane (125 g) in ethanol (250 mL) was refluxed for 16 h and worked up as described above. The product was purified by column chromatography (silica; impurities eluted with toluene–methanol–diethylamine, 70:20:10, product eluted with methanol–diethylamine, 90:10) to yield 17 g (37%) of chromatographically pure *trans*-1-[2-[(3-aminopropyl)amino]ethyl]-4-[3-(4-fluorophenyl)-6-fluoro-1-indanyl]piperazine. A mixture of this base (5 g, 0.012 mol) and urea (1.5 g, 0.025 mol) in *n*-hexane was kept at 140 °C for 3 h and then refluxed for 2 h. The reaction mixture was worked up as described in the previous example to yield 5 g of an oil. The base was converted to the dimaleate salt, which was recrystallized from ethanol–ether to give 3.0 g (38%) of **19**·dimaleate, mp 163–167 °C. Anal. ($C_{33}H_{38}F_2N_4O_9 \cdot 0.3H_2O$) C, H, N. KF determination 0.45% H_2O.

1-[2-(4-Benzyl-1-piperazinyl)ethyl]-2-imidazolidinone (28). A mixture of 1-benzylpiperazine (15 g, 0.1 mol), sodium carbonate (10.6 g, 0.1 mol), and potassium iodide (0.1 g) was refluxed with stirring for 16 h. The mixture was filtered warm, and the crystals that precipitated from the cooled filtrate were separated and recrystallized from ethyl acetate (100 mL) to give 18.8 g (65%) of **28**, mp 118 °C. Anal. ($C_{16}H_{24}N_4O$) C, H, N.

1-[2-(4-Benzoyl-1-piperazinyl)ethyl]-2-imidazolidinone (29). To a solution of **28** (10 g, 0.035 mol) in ethanol (100 mL) was added 5% Pd/C (2 g) whereupon the mixture was hydrogenated at 3 psi in a Parr apparatus for 2 h. The mixture was filtered and evaporated in vacuo. The residue was treated with ethyl acetate to give 5.9 g (86%) of 1-[2-(1-piperazinyl)ethyl]-2-imidazolidinone, mp 141–143 °C.

Benzoyl chloride (4 g, 0.029 mol) was added to a solution of the debenzylated derivative (5 g, 0.025 mol) in methylene chloride (60 mL), and the mixture was refluxed for 2 h. The reaction mixture was cooled and treated with dilute ammonium hydroxide. The organic phase was separated, dried ($MgSO_4$), and evaporated in vacuo. The residue crystallized from ethyl acetate to give 2.4 g (31%) of **29**, mp 110–111 °C. Anal. ($C_{16}H_{22}N_4O_2$) C, H, N. Compound **30** was obtained in a similar way from 4-fluorobenzoyl chloride and debenzylated derivative, mp 144–145 °C. Anal. ($C_{16}H_{21}FN_4O_2$) C, H, N.

1-[2-[4-(1-Indanyl)-1-piperazinyl]ethyl]-2-imidazolidinone (31). Thionyl chloride (26 mL) was added to a solution of 1-indanol (26 g, 0.19 mol) in ether, kept at 10–15 °C. The mixture was stirred for 2 h at 15 °C and then poured into ice water. The organic phase was separated, dried over $MgSO_4$, and evaporated in vacuo to give 27 g (91%) of crude 1-chloroindan.

A mixture of this 1-chloroindan (27 g, 0.18 mol), 1-[2-(1-piperazinyl)ethyl]-2-imidazolidinone (42 g, 0.21 mol), and potassium carbonate (35 g, 0.25 mol) in acetone (500 mL) was refluxed for 16 h. The reaction mixture was cooled, filtered, and worked up as described for **24** to give a crystalline base, which was recrystallized once from ethyl acetate to give 18 g (32%) of **31**, mp 131–132 °C. Anal. ($C_{18}H_{26}N_4O$) C, H, N.

Optical Resolutions. (+)-2 and (−)-2. A mixture of **2** (37 g, 0.091 mol) and (−)-*O*,*O*′-dibenzoyl-L-tartaric acid hydrate ((−)-DBT) (34 g, 0.091 mol) in methanol (300 mL) was heated until a clear solution was obtained. The mixture was kept in a refrigerator (at 5 °C) for 5 h. The crystals were filtered and recrystallized from ethyl acetate–methanol to give 28 g of (+)-**2**, (−)-DBT, mp 131–134 °C. The salt was converted to the base with concentrated ammonium hydroxide and extracted with ethyl acetate, and the extract was dried ($MgSO_4$) and evaporated in vacuo. The resulting oil was crystallized from ether–isopropyl ether to give 14 g of (+)-**2**, mp 89–90 °C; $[\alpha]^{22}_D$ +16.0° (*c* 1, MeOH). Anal. ($C_{24}H_{29}FN_4O$).

The first filtrate from the (−)-DBT salt was evaporated in vacuo and converted to the base to give 20.6 g of an oil, which was dissolved in methanol (150 mL) and treated with 19 g of (+)-*O*,*O*′-dibenzoyl-D-tartaric acid hydrate ((+)-DBT). The salt was isolated and recrystallized as described for the (−)-DBT salt, giving 23 g of (−)-**2**, (+)-DBT, mp 135–138 °C. The salt was converted to the base and crystallized from ether–isopropyl ether to give 9.5 g of (−)-**2**, mp 84–86 °C; $[\alpha]^{22}_D$ −15.9° (*c* 4, MeOH). Anal. ($C_{24}H_{29}FN_4O \cdot 0.3H_2O$). KF determination 1.3% H_2O.

Enantiomeric purity was determined by HPLC using a commercially available α-acid glycoprotein column [(diethylamino)ethyl silica, 10 μm, with ionic bond α-acid glycoprotein, Enantiopak LKB 100 × 4.0 mm i.d., Pharmacia LBK-Biotechnology]: mobile phase, 2-propanol–phosphate buffer, pH 6.0, 3:97; flow 0.5 mL/min; detection UV 229 nM; room temperature. The enantiomeric purities given below are in % w/w.

The enantiomeric purity of (+)-**2** was determined to be 99.6% by this method. Due to the low capacity of the α-glycoprotein column, it was impossible to determine the purity of (−)-**2** under similar conditions.

Compounds **7**, **14**, and **24** were resolved as described for **2** with (−)- and (+)-DBT. The data for the enantiomers were as follows (also see Table I). (+)-**7**: $[\alpha]^{22}_D$ +10.4° (*c* 1, dimethylformamide). (−)-**7**: $[\alpha]^{22}_D$ −10.7° (*c* 1, dimethylformamide). (+)-**14**: $[\alpha]^{22}_D$ +11.2° (*c* 5, MeOH). (−)-**14**: $[\alpha]^{22}_D$ −10.6° (*c* 5, MeOH). The enantiomeric purities of these compounds could not be determined by the HPLC method (no separation). (+)-**24**: $[\alpha]^{22}_D$ +3.8° (*c* 1, MeOH); enantiomeric purity 98%. (−)-**24**: $[\alpha]^{22}_D$ −3.4° (*c* 1, MeOH); enantiomeric purity >98%.

Compounds **6** and **12** were resolved in principle as described for **2**, except that L-(+)- and D-(−)-tartaric acid were used instead of (−)- and (+)-DBT. (+)-**6**: $[\alpha]^{22}_D$ +3.0° (*c* 1, MeOH); enantiomeric purity ca. 98%. (−)-**6**: $[\alpha]^{22}_D$ −3.1° (*c* 1, MeOH); enantiomeric purity ca. 90%. (+)-**12**: $[\alpha]^{22}_D$ +5.9° (*c* 1, MeOH); enantiomeric purity ca. 92%.

The other enantiomer, (−)-**12**, was obtained only in a very small quantity; the enantiomeric purity was determined to ca. 84%, and therefore, the compound was not included in the pharmacological testing.

Computational Methods. The MMPMI molecular mechanics program[42,43] was used to calculate conformational energies and

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energy-minimized geometries. The molecular modelling program MIMIC[44,45] was used to construct input structures and to study molecular superimposition.

Pharmacology. Animals. The rats were male Wistar (Mol:Wist) SPF, weighing 170–340 g. The rats were housed conventionally in Macrolon type III cages in groups of four to five in animal rooms kept at 21 ± 1 °C with a relative humidity of 55 ± 5%, air exchange (16 times/h) and a day/night cycle (light on 6 a.m.–6 p.m.). They had free access to commercial food pellets and tap water. The mice were male (NMRI/BOM) SPF, weighing 18–25 g and kept under the same environmental conditions as the rats.

Inhibition of Head Twitches in Rats. Head twitches were induced by quipazine (15 μmol/kg = 5 mg/kg, sc) or by combined treatment with citalopram (25 μmol/kg = 10 mg/kg, sc), followed 15 min later by L-5-HTP (341 μmol/kg = 75 mg/kg, ip).

Test compounds were injected at appropriate times before the agonists. After quipazine or L-5-HTP administration the rats were placed individually in perspex observation cages (12 × 25 cm), four to eight animals at each dosage. Head twitches were counted 30–40 min after agonist treatment. The number of head twitches induced by quipazine in the treatment groups were expressed as percent of those observed in the control groups. L-5-HTP plus citalopram induced a variable number of head twitches in the control groups. Therefore, the inhibitory effect of test compounds was expressed by an all-or-none response. The response was considered as inhibited if maximally one head twitch was observed in each rat.[22] ED_{50} values were calculated by log-probit analysis.

Inhibition of Methyl Phenidate Induced Stereotyped Gnawing in Mice. Inhibition of gnawing behavior was studied as described by Pedersen and Christensen.[46] Briefly, test compounds were injected ip 2 h before methyl phenidate (222 μmol/kg = 60 mg/kg, sc), and two mice were placed on corrugated cardboard in each gnawing cage (12 × 25 cm). The absence or presence or gnawing was evaluated after 1 h by inspection of the corrugated cardboard.

Effect of Blood Pressure in Conscious, Spontaneously Hypertensive Rats (SHR). Nonfasted male SHR/Mol in groups of five/dose, weighing 250–350 g, were anaesthetized, and the femoral artery was cannulated. Thereafter the rats were restrained in wire cages. After anesthesia was discontinued, the animals stabilized for 1.5 h, and then the arterial pressure was continuously recorded on a multichannel recorder (Devices M 19) via a Bell and Howell transducer. Three initial values (−20, −10, and 0 min) preceded administration of the test substance. The blood pressure (systolic/diastolic pressure (SAP/DAP)) was read at intervals of 10 min after intraperitoneal or oral administration for up to 60 min.

The change in blood pressure was calculated in percent of initial values, each rat serving as its own control. The dose causing 10% reduction of blood pressure (ED_{10}) calculated in μmol/kg was calculated on the basis of the mean maximum effects.

Pressor Effects in Pithed Rats. Rats (two to five/dose group) were tracheotomized, artificially ventilated and pithed under ether anesthesia according to the Method of Møller-Nielsen and Neuhold.[47] After vagotomy both carotids were ligated, and a catheter was placed in the right one to record blood pressure (Bell and Howell (4-422) transducer, Lectromed M19 recorder). The drugs were injected into the left jugular vein, at intervals of 15 min in the following sequence: pressor substance injected twice, followed by three to four dose levels of test substance (one dose/rat), and thereafter two more doses of pressor substance. The mean pressor effect was calculated as percent of the initial mean value. Phenylephrine and 5-HT were used as pressor substance in doses causing pressor response of about 70 mmHg. When 5-HT was used as a pressor substance, the rats were adrenalectomized before starting the experiment.

Receptor Binding Studies. 5-HT_2 Receptors. Inhibition of [^{3}H]ketanserin or [^{3}H]spiperone binding to rat cortial membranes (membrane extracts) was determined as described by Hyttel[48] and Hyttel and Larsen,[49] respectively.

α_1 Adrenoceptors. Inhibition of [^{3}H]prazosin binding to rat brain membranes was determined as described by Hyttel and Larsen[49] or Skarsfeldt and Hyttel.[50]

DA Receptors. Inhibition of [^{3}H]spiperone binding to D-2 receptors in rat striatal membranes was determined as described by Hyttel.[48]

Uptake Inhibition in Vitro. Inhibition of DA, NE, and 5-HT uptake in vitro was measured as previously described.[11]

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Registry No. **1**, 116842-47-8; **1**·2 maleate, 116842-48-9; **2**, 104113-54-4; (+)-**2**, 96478-43-2; (−)-**2**, 104153-48-2; (+)-2·(−)-DBT, 104113-55-5; (−)-2·(+)-DBT, 104194-85-6; **3**, 116842-49-0; **3**·2HCl, 116842-50-3; **4**, 116842-51-4; **5**, 116842-52-5; **6**, 116842-53-6; **6**·2 maleate, 116842-54-7; (+)-**6**, 116909-09-2; (−)-**6**, 116909-10-5; (+)-**6**·2 maleate, 116946-67-9; (−)-**6**·2 maleate, 116946-68-0; **7**, 80274-15-3; (+)-**7**, 104087-13-0; (−)-**7**, 104087-15-2; (+)-**7**·2 maleate, 104087-14-1; (−)-**7**·2 maleate, 104087-16-3; **8**, 104087-43-6; **8**·2HCl, 104087-23-2; **9**, 104087-44-7; **9**·2HCl, 80274-14-2; **10**, 104087-51-6; **10**·2HCl, 104087-31-2; **11**, 104087-63-0; **11**·2 maleate, 104104-65-6; **12**, 116842-55-8; (+)-**12**, 104087-58-3; (−)-**12**, 116909-11-6; (+)-**12**·2 maleate, 104087-59-4; **13**, 104087-46-9; **13**·2HCl, 104087-24-3; **14**, 104104-63-4; (+)-**14**, 104087-18-5; (−)-**14**, 104087-19-6; **14**·2HCl, 104087-17-4; **15**, 104089-91-0; **15**·2HCl, 104087-25-4; **16**, 104087-47-0; **16**·2HCl, 104087-26-5; **17**, 104087-48-1; **17**·2HCl, 104087-27-6; **18**, 104087-49-2; **18**·2HCl, 104087-28-7; **19**, 104139-54-0; **19**·2 maleate, 104139-55-1; **20**, 104104-66-7; **20**·2 maleate, 116842-56-9; **21**, 104087-50-5; **21**·2HCl, 104087-29-8; **22**, 104087-52-7; **22**·2HCl, 104087-32-3; **23**, 104087-30-1; *trans*-**24**, 104087-11-8; *cis*-**24**, 104087-12-9; (+)-**24**, 116909-12-7; (−)-**24**, 116909-13-8; **24**·2HCl, 116842-57-0; *trans*-**24**·2 maleate, 116842-58-1; *cis*-**24**·2 maleate, 116842-59-2; (+)-**24**·2 maleate, 116946-69-1; (−)-**24**·2 maleate, 116946-70-4; **25**, 80273-08-1; **26**, 85663-24-7; (+)-**26**, 80274-49-3; (−)-**26**, 80274-52-8; **27**, 104113-56-6; **28**, 116842-60-5; **29**, 116842-61-6; **30**, 116842-62-7; **31**, 116842-63-8; **I** (R^1 = F, R^2 = 4-F), 80274-59-5; **I** (R^1 = H, R^2 = 4-Cl), 116842-64-9; **I** (R = H, R^2 = 4-OMe), 116842-65-0; **I** (R^1 = H, R^2 = 2-F), 116842-66-1; **III** (R^1 = F), 80273-31-0; **III** (R^1 = H), 80273-08-1; **IV** (R^1 = F)·HCl, 116842-67-2; **IV** (R^1 = H), 116842-68-3; **V** (R^1 = F, *M* = 2), 104087-54-9; **V** (R^1 = F, *M* = 2)·4-maleate, 104087-55-0; **V** (R^1 = F, *M* = 2)·dithiocarbamate, 116842-69-4; **V** (R^1 = F, *M* = 3), 116842-70-7; **V** (R^1 = H, *M* = 2), 116842-71-8; (−)-DBT, 2743-38-6; (+)-DBT, 17026-42-5; 5-HT, 50-67-9; MeCl, 74-87-3; $Cl(CH_2)_2OH$, 107-07-3; 1-(2-chloroethyl)-2-imidazolidinone, 2387-20-4; 3-(2-chloroethyl)-2-oxazolidinone, 2508-01-2; 3-(3-chloropropyl)-2-imidazolidenone, 53710-77-3; 1-(2-chloroethyl)-3-methyl-2-imidazolidinone, 3363-69-7; 1-(2-chloroethyl)-3-ethyl-2-imidazolidinone, 22794-68-9; 3-isopropyl-1-(2-chloroethyl)-2-imidazolidinone, 30887-26-4; 1-(2-chloroethyl)-benzimidazolin-2-one, 52548-84-2; 3-(2-chloroethyl)-2,4-1*H*,3*H*)-quinazolinidione, 5081-87-8; 1-chloro-3-(4-fluorophenyl)indan, 104087-10-7; piperazine, 110-85-0; ethylenediamine, 107-15-3; 1,3-diaminopropane, 109-76-2; urea, 57-13-6; 1-benzylpiperazine, 2759-28-6; 1-[2-(1-piperazinyl)ethyl]-2-imidazolinone, 104087-61-8; 4-fluorobenzoyl chloride, 403-43-0; 1-indanol, 6351-10-6; 1-chloroindan, 35275-62-8; L-(+)-tartaric acid, 87-69-4; D-(−)-tartaric acid, 147-71-7; 1-(2-chloroethyl)-2-pyrrolidinone, 51333-90-5; 3-(3-chloropropyl)-2-oxazolidinone, 10127-86-3.

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