modification of the United States Pharmacopoeia. In each test tube (15 mL), artificial heparinoid was dissolved in 0.8 mL of a physiological saline solution (0.016, 0.014, 0.012, 0.010, 0.008, 0.006, 0.004, 0.002, 0.001 w/v %). Physiological saline solutions of standard dextran sulfate (Meito Sangyo, NC-1020) were also prepared in nine stages of concentration in the same manner as above. To each solution were added 1.0 mL of bovine plasma that had been pretreated with sodium citrate and 0.2 mL of aqueous calcium chloride (2 w/v %), and then the mixture was allowed to stand for about 15 min. The state of coagulation in each test tube was evaluated with five steps, which were 0.0, 0.25, 0.5, 0.75, and 1.0. Concentration of the artificial heparinoid (Ca) and the standard dextran sulfate (Cs) showing the coagulation-state value of 0.5 were calculated by using logarithm. Then, the anticoagulant activity of the artificial heparinoid (Aa) was calculated according to the equation Aa = As × Cs/Ca, where As was anticoagulant activity of the standard dextran sulfate.

Acknowledgment. We thank Meito Sangyo Co., Ltd. for helpful cooperation in the physiological activity tests and for supply of NC-1020 dextran sulfate. We are grateful to Dr. Alan D. Elbein for his helpful advice.

Registry No. 1, 85553-36-2; 3, 107037-81-0; 5, 105471-72-5; 6, 87481-53-6; 7, 107037-84-3; 8, 107037-87-6; 10, 87481-54-7; 11, 107037-88-7; 12, 107037-91-2; 13, 107037-94-5.

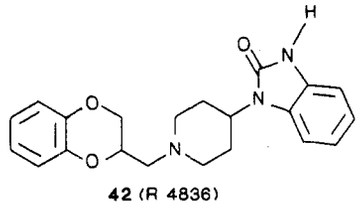
Synthesis and Neuroleptic Activity of a Series of 1-[1-(Benzo-1,4-dioxan-2-ylmethyl)-4-piperidinyl]benzimidazolone Derivatives

Rainer Henning,* Rudolf Lattrell, Hermann J. Gerhards, and Margret Leven

Hoechst AG, P.O. Box 800320, 6230 Frankfurt am Main 80, West Germany. *Received September 22, 1986*

A series of 1-[1-(benzo-1,4-dioxan-2-ylmethyl)-4-piperidinyl]benzimidazolones with various substituents in both aromatic rings have been synthesized and tested for neuroleptic activity (antiapomorphine effects and [^{3}H]spiroperidol binding) as well as extrapyramidal effects (cataleptogenic effect). A strong dependence of activity on the 5-substituent in the benzimidazolone moiety could be demonstrated. Some compounds show a large split between the desired antiapomorphine and the undesired extrapyramidal effect. From these, 1-[1-(benzo-1,4-dioxan-2-ylmethyl)-4-piperidinyl]-5-chlorobenzimidazol-2-one hydrochloride (HR 723), **12**, has been selected for further preclinical and toxicological profiling.

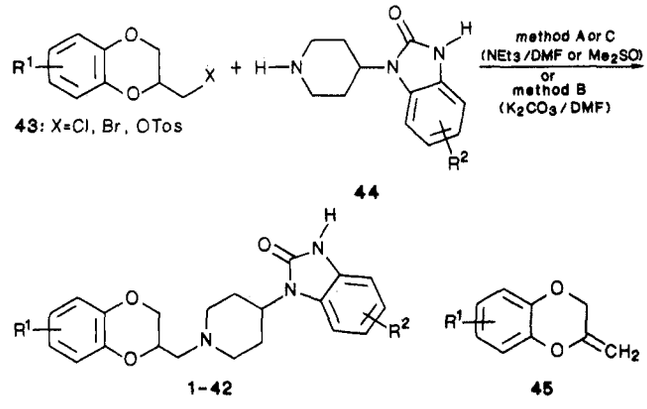
Most neuroleptic drugs that are in use in the clinical treatment of the symptoms of schizophrenia to date (e.g., butyrophenones like haloperidol and phenothiazines like chlorpromazine)[1] are plagued with the appearance of undesired and sometimes irreversible side effects, most prominently parkinson-like symptoms and tardive dyskinesia,[2] resulting from interference of these agents with dopamine receptors in the extrapyramidal system of the brain (EPS symptoms).[3] We became interested in designing potent neuroleptic agents that are less prone to the induction of these side effects. On the basis of this objective, we have designed and prepared a series of compounds containing benzo-1,4-dioxanyl and (4-piperidinyl)benzimidazolone moieties. The fully unsubstituted compound (**42**) (R 4836) has been shown to possess some neuroleptic activity.[4] Furthermore, a (4-



42 (R 4836)

piperidinyl)benzimidazolone unit occurs in potent neuroleptics such as benperidol,[5] pimozide,[6] and halopemid[7] and

Scheme I



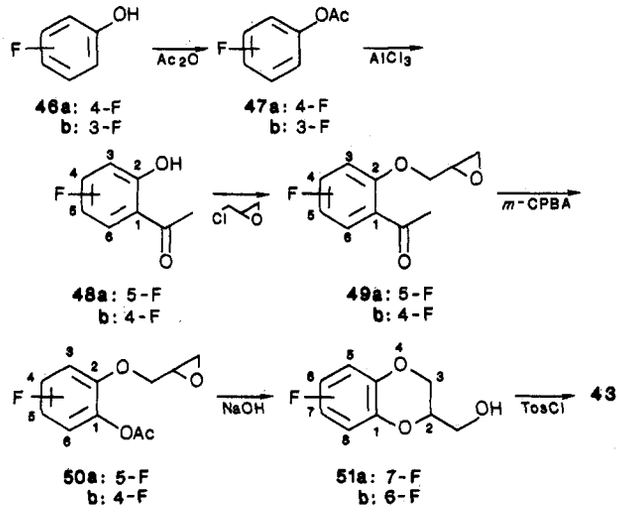
analgesics like benzitramid.[8]

The prepared compounds were subjected to screening tests for antiapomorphine activity and biochemical testing on brain dopamine receptors.[9] Activity in these tests is indicative for the clinical potency of neuroleptic drugs in schizophrenic patients.[10] Although the propensity to in-

(1) (a) Fielding, S., Lal. H., Eds. *Neuroleptics*; Futura: Mount Kisco, 1974. (b) Hoffmeister, F., Stille, G., Eds. *Psychotropic Agents*; Springer-Verlag: Berlin, 1980; Part I.
(2) (a) Diepart, E.; Cottereau, M. J.; Deniker, P. *Encephale* **1979**, *5*, 317. (b) Perris, C.; Dimitrijevic, P.; Jacobsson; L. *Br. J. Psychiatry* **1979**, *135*, 509.
(3) (a) V. Oefele, K.; Ruther, E. *Pharmacopsychiatry* **1985**, *18*, 33. (b) Borison, R. L.; Fields, J. Z.; Diamond, B. I. *Neuropharmacology* **1981**, *20*, 1321.
(4) Costall, B.; Naylor, R. J. *J. Pharm. Pharmacol.* **1978**, *30*, 693.
(5) (a) Schwarz, H. *Med. Welt* **1966**, *17*, 2642. (b) Janssen, P. A. J.; Niemegeers, C. E. J.; Schellekens, K. H. L. *Arzneim.-Forsch. (Drug Res.)* **1965**, *15I*, 104.
(6) (a) Chouinard, G.; Lehmann, H. E.; Ban, T. A. *Curr. Ther. Res.* **1970**, *12*, 598. (b) Singh, A. N. *Curr. Ther. Res.* **1971**, *13*, 695. (c) Henry, P.; Dayne, D.; Bergouignan, M. *Ann. Med.-Psychol.* **1978**, *1*, 611.
(7) Loonen, A. J. M.; van Wijngaarden, I.; Janssen, P. A. J.; Soudijn, W. *Eur. J. Pharmacol.* **1978**, *50*, 403.
(8) Knape, H. *Br. J. Anaesth.* **1970**, *42*, 325.
(9) Burt, D. R.; Creese, I.; Snyder, S. H. *Med. Pharmacol.* **1976**, *12*, 800.
(10) Vinař, O.; Kršiak, M. *The Phenothiazines and Structurally Related Drugs*; Raven: New York, 1974. Niemegeers, C. J. E.; Janssen, P. A. *J. Life Sci.* **1979**, *24*, 2201.

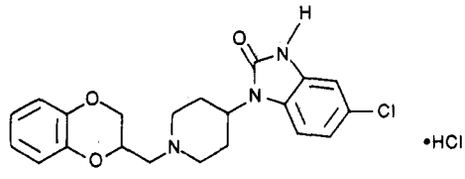
0022-2623/87/1830-0814$01.50/0

Scheme II



duce catalepsy in rats does not completely parallel the appearance of EPS in patients,[11] its predictive value is high enough to sort out candidates for in-depth evaluation.[12] Any new neuroleptic should be devoid of activity in this test model or at least show a large split between the clinically effective dose and the dose inducing catalepsy.

From the results of our screening tests, it has been found that 1-[1-(benzo-1,4-dioxan-2-ylmethyl)-4-piperidinyl]-5-chlorobenzimidazol-2-one hydrochloride (**12**) (HR 723) is



12 (HR 723)

most favorable in this respect, being about equipotent to haloperidol in suppressing apomorphine-induced climbing in mice while inducing catalepsy in rats in a dose that is more than 100-fold higher than that of haloperidol.

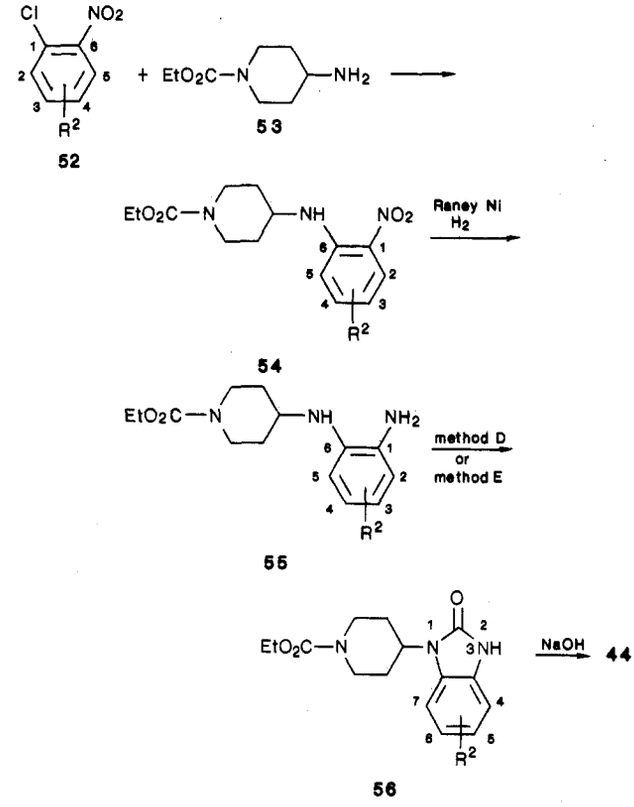
The synthesis and antiapomorphine structure–activity relationships of this series are discussed in this paper.

Chemistry

Compounds **1–42** are assembled from 2-(halomethyl)- or 2-[(tosyloxy)methyl]-1,4-benzodioxans (**43**) with appropriate substituents in the aromatic ring with 1-(4-piperidinyl)benzimidazolones (**44**) in the presence of a base (Scheme I). Either NEt_3 in DMF or Me_2SO (method A or C) or K_2CO_3 in DMF (method B) is the most satisfactory condition under which β-elimination affording vinyl ether **45** is minimized.

Several halides and tosylates (**43**; R^1 = 5-CH_3, 6-CH_3, 6,7-$(CH_3)_2$, 7-Cl, 6,7-Cl_2)[13] have been prepared for other

Scheme III



purposes and are known from the literature. The 6- and 7-fluoro analogues are new and prepared according to Scheme II.

p-Fluorophenol (**46a**) is acetylated and the ester (**47a**) subjected to Fries rearrangement to give hydroxyacetophenone **48a**.[14] Etherification with epichlorohydrin to give **49a** followed by Baeyer–Villiger oxidation affords **50a**, in which ring closure takes place upon saponification to give alcohol **51a**, which finally tosylated to give **43a** (R^1 = 7-F). Compound **43b** (R^1 = 6-F) is obtained according to the same scheme with *m*-fluorophenol as the starting material.

A few 1-(4-piperidinyl)benzimidazolones **44** have appeared in the patent literature; their synthesis has been generalized (Scheme III).[15]

o-Chloronitrobenzenes **52** are condensed with the known protected 4-aminopiperidine **53**.[15] The nitro group in **54** is reduced to **55** with hydrogen and Raney nickel as catalyst. Ring closure to **56** is effected with either phosgene (method D) or urea (method E) followed by alkaline hydrolysis of the urethane protecting group. In the case of the 5-fluoro or 5-bromo compounds **56**, the respective 1,4-dihalo-2-nitrobenzenes are used as starting compounds.

Some of the required *o*-chloronitrobenzenes **52** are not commercially available and are prepared according to literature procedures (R^2 = 4-$C(CH_3)_3$,[16] 4-C_2H_5,[17] 4-C_6H_5[17]). In the case of **44** (R^2 = 5-NH_2), the synthesis

(11) (a) Jenner, P.; Elliot, P. N. C.; Clow, A.; Reavill, C.; Marsden, C. D. *J. Pharm. Pharmacol.* **1978**, *30*, 46. (b) Jenner, P.; Marsden, C. D. *Sulpiride and other Benzamides*; Spano, P. F., Trabucchi, M., Corsini, G. V., Gessa, G. L., Eds.; Italian Brain Research Foundation: Milan, 1979; p 119.

(12) (a) Wise, L. D.; Pattison, I. C.; Butler, D. E.; De Wald, H. A.; Lewis, E. P.; Lobbestael, S. J.; Tecle, H.; Coghenour, L. L.; Downs, D. A.; Poschel, B. P. H. *J. Med. Chem.* **1985**, *28*, 1811. (b) Van Rossum, J. M.; Boissier, J. R.; Janssen, P. A. J.; Julou, L.; Loew, D. M.; Moller Nielsen, I.; Munvad, I.; Randrup, A.; Stille, G.; Tedeschi, D. H. *Pharmacology of Neuroleptic Drugs. Modern Problems of Pharmacopsychiatry (Neuroleptics)*; Bobon, J., Janssen, P. A. J., Eds.; S. Karger: Basel, 1970; p 23.

(13) Augstein, J.; Green, S. M.; Munro, A. M.; Potter, G. W. H.; Worthing, C. R.; Wrigley, T. *J. Med. Chem.* **1965**, *8*, 446 and literature cited therein.

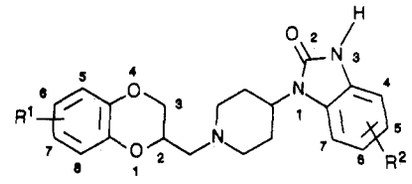
(14) Modification of a procedure in: Corse, J.; Ingraham, L. I. *J. Org. Chem.* **1951**, *16*, 1345.

(15) Vandenberk, J.; Kennis, L. E. J.; van der Aa, M. J. M. C.; van Heertum, A. H. M. T.; German Pat. Appl. 2645125. Janssen, P. A. J.; van Wijngaarden, I.; Soudijn, W. German Pat. Appl. 2400094.

(16) Lambooy, J. P. *J. Am. Chem. Soc.* **1958**, *80*, 110.

(17) Greizerstein, W.; Bonelli, R. A.; Brieux, J. A. *J. Am. Chem. Soc.* **1962**, *84*, 1026.

Table I. Chemical and Pharmacological Data of 1-[1-(Benzo-1,4-dioxan-2-ylmethyl)piperidinyl]benzimidazolones 1–42



1-42

compd	R^1	R^2	method[a]	%	mp,[b] °C	recrystn solvent[c]	formula	inhibn of climbing:[d] ED_{50}, mg/kg ip
1	H	5-NH_2	C	5	214–215 dec (a)	A	$C_{21}H_{24}N_4O_3$·HCl	3.9
					>220 dec (b)	B		
2	H	5-Br	C	60	214–216 (a)	C	$C_{21}H_{22}BrN_3O_3$·HCl·$(CH_3)_2CO$	0.082 (0.035–0.192)
					>200 dec (b)	B		
3	H	5-OCH_3	C	28	177–181 (a)	C	$C_{22}H_{25}N_3O_4$·HCl	0.0096
					220–223 dec (b)	B		(0.0033–0.278)
4	H	6-Cl, 7-CH_3	B_1	30	187 (a)	A	$C_{22}H_{24}ClN_3O_3$·HCl	10
					254–255 (b)	B		
5	H	5-CF_3	B_2	24	104 dec (a)	A	$C_{22}H_{22}F_3N_3O_3$·HCl	>10
					243–247 (b)	B		
6	H	5-F	B_2	37	174–184 (a)	D	$C_{21}H_{22}FN_3O_3$·HCl·H_2O	0.019 (0.009–0.037)
					169 dec (b)	B		
7	H	7-aza	B_1	10	240 dec (b)	E	$C_{20}H_{22}N_4O_3$·HCl	>10
8	H	5,6-Cl_2	B_1	21	207–211 (a)	A	$C_{21}H_{21}Cl_2N_3O_3$·HCl·$2H_2O$	0.45
					218–222 (b)	B		
9	H	5-CH_3	B_1	38	209–215 (a)	C	$C_{22}H_{25}N_3O_3$·HCl·$0.5H_2O$	0.013 (0.007–0.250)
					212–214 (b)	C		
10	H	7-Cl	B_1[e]	27	171–174 (a)	C	$C_{21}H_{22}ClN_3O_3$·HCl	>20
					236 (b)	B		
11	H	6-Cl	B_1	43	232–234 (a)	C	$C_{21}H_{22}ClN_3O_3$·HCl·$0.5H_2O$	0.11
					230–232 dec (b)	C		
12	H	5-Cl	A	60	226–228 (a)	C	$C_{21}H_{22}ClN_3O_3$·HCl	0.09 (0.02–0.42)
					196–200 dec (b)	B		0.21 (0.11–0.41) (po)
13	H	5-$C(CH_3)_3$	C	20	>250 dec (a)	B	$C_{25}H_{31}N_3O_3$·HCl·H_2O	>25
					182 (b)	A		
14	H	5-C_2H_5	C	23	163 (a)	A	$C_{23}H_{27}N_3O_3$·HCl	0.17
					250 (b)	B		
15	H	5-C_6H_5	C	38	164 (a)	A	$C_{27}H_{27}N_3O_3$·HCl	>25
					>240 dec (b)	B		
16	6-F	5-CH_3	C	49	210–215 (a)	C	$C_{22}H_{24}FN_3O_3$·HCl·$0.5H_2O$	0.5
					260–262 dec (b)	B		
17	6-F	5-F	C	20	209 (a)	D	$C_{21}H_{21}F_2N_3O_3$·HCl	0.63
					237 (b)	B		
18	6-F	5-Cl	C[f]	19	213–217 (a)	C	$C_{21}H_{21}FClN_3O_3$·HCl	0.2
					262–265 (b)	E		
19	7-F	5-F	C	32	140 dec (a)	A	$C_{21}H_{21}F_2N_3O_3$·HCl	0.098 (0.037–0.256)
					247–250 (b)	B		
20	7-F	7-aza	C	35	150 dec (a)	A	$C_{20}H_{21}FN_4O_3$·HCl	>25
					205–210 (b)	B		
21	7-F	6-Cl, 7-CH_3	C	43	201–203 (a)	D	$C_{22}H_{23}ClFN_3O_3$·HCl	>25
					251–255 (b)	B		
22	7-F	5,6-Cl_2	C	53	235–237 (a)	C	$C_{21}H_{20}Cl_2FN_3O_3$·HCl·H_2O	1.4
					258–261 (b)	B		
23	7-F	5-CH_3	C	48	231 (a)	D	$C_{22}H_{24}FN_3O_3$·HCl	0.014 (0.007–0.029)
					293–295 (b)	B		
24	7-F	7-Cl	C	35	174–176 (a)	C	$C_{21}H_{21}ClFN_3O_3$·HCl	>25
					242–251 (b)	B		
25	7-F	6-Cl	C	51	233–235 (a)	C	$C_{21}H_{21}ClFN_3O_3$·HCl·$0.5H_2O$	0.16
					227 dec (b)	E		
26	7-F	5-CF_3	C	22	115–118 (a)	F	$C_{22}H_{21}F_4N_3O_3$·HCl	>10
					170–173 (b)	E		
27	7-F	5-Cl	C	57	232–234 (a)	G	$C_{21}H_{21}ClFN_3O_3$·HCl	0.14 (po)
					230–232 dec (b)	B		
28	7-Cl	5-CH_3	C	30	187 (a)	D	$C_{22}H_{24}ClN_3O_3$·HCl	0.093 (0.047–0.183)
					245 dec (b)	B		
29	7-Cl	5-F	C	35	152–154 (a)	C	$C_{21}H_{21}ClFN_3O_3$·HCl·$0.5H_2O$	0.044 (0.03–0.064)
					233–236 (b)	B		
30	7-Cl	5-Cl	C	41	184–189 (a)	C	$C_{21}H_{21}Cl_2N_3O_3$·HCl	0.75
					>180 dec (a)	B		
31	6,7-Cl_2	5-CH_3	C	49	240 dec (a)	C	$C_{22}H_{23}Cl_2N_3O_3$·HCl	3.6
					265–270 dec (b)	B		
32	6,7-Cl_2	5-F	C	17	199–201 (a)	C	$C_{21}H_{20}Cl_2FN_3O_3$·HCl·$(CH_3)_2CO$	5.5
					>240 dec (b)	B		
33	6,7-Cl_2	5-Cl	C	47	238–240 (a)	C	$C_{21}H_{20}Cl_3N_3O_3$·HCl·H_2O	6.0
					289–290 (b)	B		
34	5-CH_3	5-F	C	14	296 (b)	B	$C_{22}H_{24}FN_3O_3$·HCl	0.043 (0.019–0.092)

Table I (Continued)

compd	R^1	R^2	method[a]	%	mp,[b] °C	recrystn solvent[c]	formula	inhibn of climbing:[d] ED_{50}, mg/kg ip
35	5-CH_3	5-Cl	C	20	175 (a)	A	$C_{22}H_{24}ClN_3O_3 \cdot HCl \cdot 0.5HCl$	1.3
					>280 dec	B		
36	6-CH_3	5-CH_3	C	43	144–146 (a)	A	$C_{23}H_{27}N_3O_3 \cdot HCl$	0.032 (0.009–0.109)
					>179 dec (b)	B		
38	6-CH_3	5-Cl	C	43	164–166 (a)	A	$C_{22}H_{24}ClN_3O_3 \cdot HCl$	0.121 (0.071–0.206)
					224–226 (b)	B		
39	6,7-$(CH_3)_2$	5-CH_3	C	51	220–225 (a)	C	$C_{24}H_{29}N_3O_3 \cdot HCl$	0.079 (0.008–0.766)
					208–210 (b)	B		
40	6,7-$(CH_3)_2$	5-F	C	28	235–237 (a)	C	$C_{23}H_{26}FN_3O_3 \cdot HCl \cdot 0.5H_2O$	0.055 (0.040–0.075)
					>190 dec (b)	B		
41	6,7-$(CH_3)_2$	5-Cl	C	55	226 (a)	C	$C_{23}H_{26}ClN_3O_3 \cdot HCl \cdot 0.5H_2O$	0.8
					>205 dec (b)	B		
42	H (R 4836)	H	A	33	183–184 (a)	C	$C_{21}H_{23}N_3O_3 \cdot HCl$	0.7
					193–195 (b)	B		
haloperidol								0.06 (0.04–0.09)
								0.09 (0.05–0.17)

[a] See Experimental Section. [b] (a) free base, (b) hydrochloride. [c] A, diethyl ether; B, acetone; C, ethyl acetate; D, ethyl acetate/diethyl ether; E, ethyl acetate/acetone; F, diisopropyl ether; G, dichloromethane/ethyl acetate. [d] ED_{50}, the dose that inhibits induction of climbing behavior in 50% of the mice, was estimated by linear regression; 95% confidence limits are included in parentheses for the most potent compounds. [e] Eight millimoles of *N*-ethylmorpholine was used instead of K_2CO_3. [f] Thirty-two millimoles of K_2CO_3 was used instead of triethylamine.

starts with 4-chloro-3-nitroacetanilide (**52**, R^2 = 4-$NHCOCH_3$); the acetamide group is hydrolyzed together with the urethane in the final step (**56** → **44**).

Pharmacology and Structure–Activity Discussion

The neuroleptic activity of the present compounds was determined by their inhibitory effect on apomorphine-induced climbing behavior in mice. Their ability to induce extrapyramidal effects was estimated for the most potent compounds by their potency in induction of catalepsy in rats. These methods are described in the Experimental Section. Also, their affinity to brain dopamine receptors was investigated by displacement of [^{3}H]spiroperidol form bovine nucleus caudatus membranes. The major aim of the study was the systematic evaluation of the effects of substituents in both aromatic rings on neuroleptic potency.

The influence of substituents in the benzodioxan moiety will be discussed first. The potency in this series (**1–42**, Table I) decreases in the order R^1 = H > 7-F ≈ 6-CH_3 ≥ 6-F > 7-Cl ≈ 6,7-$(CH_3)_2$ ≥ 5-CH_3 > 6,7-Cl_2. Since with the exception of the dichloro compound these effects are not very large, they cannot be attributed unequivocally to either electronic or steric influences. The latter seems to predominate, however, since the most potent compounds come from the unsubstituted series (**2, 6, 9–12**) followed by the fluorine-substituted derivatives (**19, 23**). Compounds with a methyl group in the 5-position (**35**) are somewhat less potent, whereas the activity of the bulky dichloro compounds (**31–33**) is decreased by 1 order of magnitude.

The effects of substituents R^2 in the benzimidazole benzo-fused ring are much more pronounced. We find, that the antiapomorphine activity of the unsubstituted compound **42**, which has been described in the literature[4] can be greatly enhanced by introduction of a variety of groups in the 5-position. The most potent derivative carries a 5-methoxy substituent (**3**); it is almost 100-fold more potent compared with **42**. The order of activity of the 5-substituents is shown most clearly in the series that is unsubstituted in the benzodioxan ring; it decreases with R^2 = OCH_3 > CH_3 ≥ F > Cl = Br > C_2H_5 > NH_2 (**3, 9, 6, 12, 2, 14, 1**, respectively).

The same order is essentially followed in the other series also. Substitution of the benzimidazolone ring with the very bulky *tert*-butyl (**13**) and phenyl (**15**) groups as well as the strongly electron withdrawing CF_3 group (**5**) abolishes the activity completely. It is also quite clear that increase in size of a 5-alkyl group diminishes the potency (R^2 = CH_3 > C_2H_5 ≫ $C(CH_3)_3$). Substituents that increase electron density in the phenyl ring by a mesomeric effect seem to be suited best, even though with this explanation the activity of the 5-amino compound **1** is inexplicably low. Surprisingly, this compound has a quite strong α-sympathicolytic effect as judged by the inhibition of norepinephrin toxicity (data not shown).

Substituents in other positions of the benzo-fused benzimidazolone ring give much less favorable results. A chlorine atom at C-6 is still tolerated fairly well (compounds **8, 11**), but substituting the 7-position leads to complete loss of activity (compounds **4, 10**). The same is true for the pyridine analogue **7**, which is not surprising judged by the low electron density of the pyridine ring.

As seen in Table II, the most potent compounds of the present series have quite large variations in their liability to induce cataleptic effects in rats. No clear-cut structure–activity relationship can be deduced for the cataleptogenic activity. The most potent compounds in this respect are **3** and **28**. In general, substitution of the benzodioxan by F or Cl seems to increase the liability for the induction of this side effect (compare **9, 23, 28**). The best compounds (**2, 9, 12**, and **40**) show a large split compared with haloperidol.

Table II also lists the inhibitory constants for the displacement of [^{3}H]spiroperidol (see Experimental Section). Although all the compounds were active in this affinity test for D_2 dopamine receptors,[18] no good correlation between these values and the ED_{50} for antiapomorphine activity could be detected. This suggests that distribution to the receptor sites in the brain plays an important role in the determination of the in vivo potency.

From the most selective compounds (**2, 9, 12**, and **40**) **12** (HR 723) has been selected for further preclinical evaluation, as it is expected to be a potent neuroleptic with fewer side effects than other drugs of this kind.

Experimental Section

Melting points were measured with a Büchi 510 melting point apparatus and are uncorrected. The structures of all compounds were supported by NMR and mass spectroscopy. NMR spectra were recorded with a Bruker WP 60 with Me_4Si as internal

(18) For the relevance of D_2 dopamine receptors for neuroleptic activity, see: (a) Sethy, V. H.; *Eur. J. Pharmacol.* **1979**, *60*, 397. (b) Seeman, P. *Pharmacol. Rev.* **1981**, *32*, 229.

Table II. Comparison of Spiroperidol Binding, Climbing Inhibition, and Induction of Catalepsy for Selected Compounds from Table I

compd	inhibn of spiroperidol binding: K_i, μM	inhibn of climbing: ED_{50}, mg/kg	induction of catalepsy: ED_{50}, mg/kg	ED_{50} (catalepsy)/ ED_{50} (climbing)[a]
2	0.07	0.082	20	244
3	0.15	0.0096	1	104
9	0.12	0.013	40	3077
12	0.03	0.09	>40	>444
17	0.07	0.63	<5	<8
19	n.d.	0.098	20	204
23	0.15	0.014	2.5	187
28	0.03	0.093	1	11
34	0.008	0.043	8	186
36	0.04	0.032	6	188
38	0.06	0.121	20	165
39	0.045	0.079	10	126
40	0.025	0.055	>20	>363
haloperidol	0.02	0.06	0.5	8

[a] This ratio can only be considered as a crude measure for the therapeutic ratio, since the models involve different animal species. In other rat models, however, **12** was equally potent as in the climbing model (data not shown).

standard. Mass spectra were obtained on a AEI MS 30 instrument. All solid compounds were analyzed (C, H, N) by the Hoechst Analytical Department and values obtained were within 0.4% of the theoretical values unless otherwise indicated.

Chemistry. General Procedure for the Preparation of Compounds 1–42. Method A. Both the appropriate 2-(bromomethyl)-1,4-benzodioxan (**43**) (10 mmol) and a 1-(4-piperidinyl)benzimidazolone (**44**) (10 mmol) are dissolved in 25 mL of dry dimethylformamide. A 1.4-mL sample of triethylamine and 0.3 g (2 mmol) of sodium iodide are added, and the mixture is stirred at room temperature for 60 h and then poured into water. Diisopropyl ether is added and the two-layer mixture stirred vigorously for 2 h. The solid residue is filtered off and purified by column chromatography on silica gel with ethyl acetate/methanol mixtures as eluent. The hydrochlorides are obtained by dissolving the free amine in dichloromethane/methanol, adding a slight excess of 2.5 N ethanolic HCl, removing the solvent in vacuo, and crystallizing from the appropriate solvent.

Method B_1. An appropriate 2-(bromomethyl)-1,4-benzodioxan (**43**) (8 mmol) and a 1-(4-piperidinyl)benzimidazolone (**44**) (8 mmol) are dissolved in 20 mL of dry DMF; 1.11 g (8 mmol) of K_2CO_3 and 0.4 g of NaI are added, and the mixture is heated with stirring to 120 °C for 6 h. The reaction mixture is poured into ice water and extracted three times with CH_2Cl_2. The combined extracts are washed with H_2O (6×) and dried over K_2CO_3. The crude product obtained after evaporation in vacuo is purified by crystallization from the appropriate solvent or chromatography. Hydrochlorides are obtained as described in method A.

Method B_2. The reaction mixture is heated at 50 °C for 40 h. Otherwise the conditions are identical with those described in method B_1.

Method C. An appropriate 2-[(tosyloxy)methyl]-1,4-benzodioxan (**43**) (10 mmol) and a 1-(4-piperidinyl)benzimidazolone (**44**) (10 mmol) are dissolved in 40 mL of dry Me_2SO. KI (1.99 g, 12 mmol) and 1.4 mL (10 mmol) of triethylamine are added, and the mixture is heated to 80 °C for 20 h. Workup is identical with that described in method B_1.

4-Fluorophenyl Acetate (47a). 4-Fluorophenol (100 g, 0.89 mol) is dissolved in 0.9 mol of acetic anhydride. Upon addition of 1 drop of concentrated H_2SO_4, the temperature rises to 120 °C. After being cooled, the mixture is poured into a solution of 8 g of $NaHCO_3$ in 1 L of cold water and extracted with diethyl ether. The extract is washed with saturated $NaHCO_3$ solution, dried over $MgSO_4$, and evaporated in vacuo to give 110 g (80%) of essentially pure product that is used directly in the next step.

The same procedure is used to prepare **3-fluorophenyl acetate (47b)**, which is purified by distillation, yield 87%, bp 77–78 °C (13 mm).

5-Fluoro-2-hydroxyacetophenone (48a). Crude ester **47a** (110 g, 0.7 mol) is heated together with 165 g of $AlCl_3$ at 160 °C for 2 h; the mixture is then poured on 700 g of a mixture of ice and concentrated HCl. The product is isolated by steam distillation followed by extraction of the distillate with diethyl ether and recrystallization from light petroleum to obtain pure material; yield 94 g (85%), mp 56 °C. Anal. ($C_8H_7FO_2$) C, H.

Analogously, **4-fluoro-2-hydroxyacetophenone (48b)** is obtained from **47b**, yield 90%, mp 24 °C. Anal. ($C_8H_7FO_2$) C, H.

5-Fluoro-2-(oxiranylmethoxy)acetophenone (49a). To a refluxing mixture of phenol **48a** (20.9 g, 0.14 mol) and 38 g of epichlorohydrin in 20 mL of ethanol is added a solution of 9.5 g KOH in 30 mL of ethanol and 5 mL of H_2O dropwise with vigorous stirring. After 1 h the solvent is removed in vacuo, H_2O is added, and the mixture is extracted with diethyl ether. The product is obtained as an oil and used directly in the next step without further purification; yield 25 g (88%); NMR ($CDCl_3$) δ 7.3–6.7 (m, 3), 4.4–3.6 (m, 2), 3.4–3.1 (m, 1), 2.95–2.5 (m, 2), 2.53 (s, 3, CH_3).

4-Fluoro-2-(oxiranylmethoxy)acetophenone (49b) is obtained analogously from **48b**; yield 78%; NMR ($CDCl_3$) δ 7.7 (dd, 1), 6.6 (m, 2), 4.5–3.7 (m, 2), 3.6–3.2 (m, 1), 3.1–2.6 (m, 2), 2.62 (s, 3, CH_3).

2-Acetoxy-4-fluoro-1-(oxiranylmethoxy)benzene (50a). A mixture of ketone **49a** (25 g) and 27.6 g of *m*-chloroperbenzoic acid in 300 mL of chloroform is heated at 80 °C with stirring for 6 h. Another batch of 13.8 g of peracid is added and heating is continued for 15 h. After cooling, the solution is washed with 10% $NaHSO_3$ solution (3×) and 10% $NaHCO_3$ solution (3×), dried over Na_2SO_4, and evaporated to give 21.6 g (84%) of a pale yellow oil; NMR ($CDCl_3$) δ 6.7 (m, 3), 4.3–3.6 (m, 2), 3.2 (m, 1), 2.9–2.5 (m, 2), 2.22 (s, 3, CH_3).

By the same procedure, 29.3 g (95%) of compound **50b** is obtained from 28 g of **49b**; NMR ($CDCl_3$) δ 7.0–6.5 (m, 3), 4.3–3.7 (m, 2), 3.3 (m, 1), 3.0–2.6 (m, 2), 2.3 (s, 3, CH_3).

7-Fluoro-2-(hydroxymethyl)-1,4-benzodioxan (51a). A suspension of 20 g (88 mmol) of **50a** in 36.5 mL 10% NaOH is refluxed with vigorous stirring. After being cooled, the mixture is extracted with diethyl ether (3×), and the combined ether layers are washed with H_2O and dried over Na_2SO_4. The crude brown oil is distilled to give 9.2 g (57%) of **51a**, bp 94–99 °C (0.2 mm). Anal. ($C_9H_9FO_3$) C, H.

Via the same procedure, 11.2 g (47%) **51b** is obtained from 29.3 g of **50b**, bp 90–92 °C (0.2 mm). The product crystallizes upon standing, mp 65–67 °C. Anal. ($C_9H_9FO_3$) C, H.

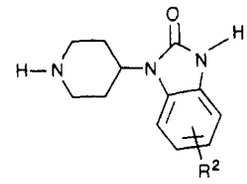
7-Fluoro-2-[(tosyloxy)methyl]-1,4-benzodioxan (43a). *p*-Toluenesulfonyl chloride (9.6 g, 50 mmol) is added to an ice-cold solution of 8.8 g (48 mmol) of **51a** in 30 mL of dry pyridine. After 5 h at ambient temperature, the solution is poured into a mixture of ice and concentrated HCl and extracted with diethyl ether (4×). The combined extracts are washed with 2 N HCl, dried over Na_2SO_4, and evaporated. The crude product is recrystallized from ethanol/light petroleum to give 12.2 g (75%) of **43a**, mp 87–89 °C. Anal. ($C_{16}H_{15}FO_5S$) C, H.

6-Fluoro-2-[(tosyloxy)methyl]-1,4-benzodioxan (43b) is obtained analogously as a viscous oil. Anal. ($C_{16}H_{15}FO_5S$) C, H.

The synthesis of 1-(4-piperidinyl)benzimidazolones is exemplified in the following for the 5-*tert*-butyl compound.

1-(Ethoxycarbonyl)-4-(2-nitro-4-*tert*-butylanilino)-piperidine (54a, R^2 = *tert*-Butyl). A mixture of 15.1 g (70.6

Table III. 1-(4-Piperidinyl)benzimidazolones **44**



compd.	R^2	yield, % 52 → 54	54 → 55	55 → 56	56 → 44	mp, °C	formula	anal.
44b	5-Br[a]	64	92	79[b]	48	209	$C_{12}H_{14}BrN_3O$	C, H, N
44c	5-OCH_3	10	70	91	31	117	$C_{13}H_{17}N_3O_2$	C, H, N
44d	6-Cl, 7-CH_3			31[b,c]	92	174–176	$C_{13}H_{16}ClN_3O$	C, H, N
44e	5-CF_3	73	83	81[b]	86	260	$C_{13}H_{14}F_3N_3O$	C, H, N
44f	5-F[f]	71	78	78[b]	88	159	$C_{12}H_{14}FN_3O$	C, H, N
44g	7-aza			57[d] 89[b]	53	173	$C_{11}H_{14}N_4O$	C, H, N
44h	5,6-Cl_2	60	73	82[b]	75	202–203	$C_{12}H_{13}Cl_2N_3O$	C, H, N
44i	5-CH_3			25[d] 94[b]	60	196–197	$C_{13}H_{17}N_3O$	C, H, N
44j	7-Cl			49[d] 78[b]	72	246	$C_{12}H_{14}ClN_3O$	C, H, N
44k	6-Cl	45	91	94[b]	87	130	$C_{12}H_{14}ClN_3O$	C, H, N
44l	5-Cl[e]	65	93	90	96	220		
44m	5-C_2H_5	24	77	80	52	200	$C_{14}H_{19}N_3O$	C, H, N
44n	5-C_6H_5	29	27	93	77	200	$C_{18}H_{19}N_3O$	C, H, N

[a] 1,4-Dibromo-2-nitrobenzene was used as starting material. [b] Ring closure is effected by melting **55** with 3 equiv of urea, taking up in boiling toluene, removing insoluble material by filtration, concentrating, and crystallizing by trituration with diethyl ether. [c] Overall yield **52** → **56**. [d] Overall yield **52** → **55**. [e] Reference 13. [f] 1,4-Difluoro-2-nitrobenzene was used as starting material.

mmol) of 4-*tert*-butyl-1-chloro-2-nitrobenzene, 12.15 g (70.6 mmol) of 4-amino-1-(ethoxycarbonyl)piperidine, 7.48 g (70.6 mmol) of Na_2CO_3, and 0.12 g (0.7 mmol) of KI in 100 mL of cyclohexanol is heated at 160 °C with stirring for 28 h. After the mixture is cooled, toluene is added and the mixture extracted with H_2O. The organic layer is dried over Na_2SO_4 and evaporated. Chromatography on 500 g of SiO_2 yields 12.6 g (51%) of orange crystalline product, mp 136–137 °C (from diisopropyl ether). Anal. ($C_{18}H_{27}N_3O_4$) C, H, N.

4-(2-Amino-4-*tert*-butylanilino)-1-(ethoxycarbonyl)-piperidine (55a, R^2 = *tert*-Butyl). Compound **54a** (R^2 = *tert*-butyl) (3.1 g, 8.8 mmol) is dissolved in a mixture of 10 mL of dry ethanol and 20 mL of THF. After addition of 1 g of Raney Ni, hydrogen is introduced at a pressure of 1.2 bars (room temperature). After 1 h, 560 mL of H_2 is absorbed. Filtration and evaporation gave 2.6 g (92.5%) of colorless crystals, mp 115 °C (from diisopropyl ether). Anal. ($C_{18}H_{29}N_3O_2$) C, H, N.

1-[1-(Ethoxycarbonyl)-4-piperidinyl]-5-*tert*-butylbenzimidazolone (56a, R^2 = *tert*-Butyl). A 10% solution of phosgene in CH_2Cl_2 (6 mL) is added dropwise at 0 °C to a solution of **55a** (R^2 = *tert*-butyl), followed by addition of 2.2 mL (16 mmol) of triethylamine. After 30 min the mixture is transferred to a separatory funnel and washed with 1 N HCl and H_2O, dried over Na_2SO_4, and evaporated. The product crystallizes upon trituration with diethyl ether; yield 2.5 g (90%), mp 199–200 °C. Anal. ($C_{19}H_{27}N_3O_3$) C, H, N.

1-(4-Piperidinyl)-5-*tert*-butylbenzimidazolone (44a, R^2 = *tert*-Butyl). Compound **56a** (R^2 = *tert*-butyl, 2.5 g) is heated to reflux with 30 mL of 10% NaOH for 8 h. After being cooled, the mixture is made strongly acidic with concentrated HCl. The pH is then adjusted to 10 with solid Na_2CO_3 (*caution: extensive foaming*!). The precipitated product is filtered with suction, washed with water, and dried in vacuo at 50 °C to give 1.64 g (83.2%) of colorless crystals, mp 238.5 °C. Anal. ($C_{16}H_{23}N_3O$) C, H, N.

Other compounds **44** obtained by the same sequence of reactions are compiled in Table III.

Pharmacology. Inhibition of Apomorphine-Induced Climbing Behavior in Mice. CD-1 male mice are placed in pairs in wire mesh cages (12 × 12 × 20 cm) and are allowed 1 h for adaption and exploration of the new environment. Apomorphine (1.5 mg/kg) is injected sc. This dose causes climbing in all subjects for 30 min. The test compound is injected ip 60 min prior to the apomorphine challenge. For evaluation of climbing, three readings are taken at 10, 20, and 30 min after apomorphine administration (scoring scale: four paws on bottom (no climbing), 0; two paws on the wall (rearing), 1; four paws on the wall (full climbing), 2). Mice consistently climbing before apomorphine injection are discarded. The climbing scores are individually totalled (maximum score: 6 per mouse) and the total score of the control (vehicle ip–apomorphine sc) is set to 100%. ED_{50} values with 95% confidence limits are calculated by linear regression analysis (log dose transformation) using 8 to 16 mice per dose.

Catalepsy in Rats. Induction of catalepsy was tested in male Wistar rats 1, 2, 3, 4, and 6 h after oral administration of the test compound. The rats are placed with the forepaws onto a bar situated 7 cm above the floor of a perspex jar (22 × 38 × 16 cm) and tested for catalepsy according to a rating score (time resting upon the bar: 10 s, 0; 10–20 s, 1; 20–30 s, 2; >30 s, 3). Testing was repeated two times for each animal in 2-min intervals. The cumulated maximal score for one animal during the 6-h observation period is 45. Scores are expressed as percent of the maximal score obtainable, and ED_{50} values are calculated by linear regression analysis with four rats per dose.

Inhibition of [^{3}H]Spiroperidol Binding. Membrane fractions of bovine caudate nucleus were prepared according to the method described[9] and stored at −40 °C. For an experiment, fractions are thawed, incubated for 5 min at 37 °C, and centrifuged at 50000*g* for 10 min. The precipitate is resuspended in buffer to a final dilution of 1:1000 with reference to the starting material. This suspension is incubated with 1 nM (39 Ci/mmol) spiroperidol and split into 5.0-mL fractions. In each experiment, the following are incubated: three samples with 10^{-5} M butaclamol to determine unspecific binding, three samples without further additive to determine total binding, and one sample each for different concentrations of the test compound. The incubation is stopped by cooling in an ice bath. The samples are diluted with 3.0 mL of ice-cold buffer, filtered, and washed with a Skatron cell collector through glass fiber mats GF/F. The filters are air-dried and mixed with 5 mL of scintillation cocktail. After 10 min of shaking and cessation of chemoluminescence, the samples are counted. The replacement in percent of specific binding of the control are calculated for the different concentrations, and the IC_{50} is determined from at least three independent experiments via graphic interpolation. For calculation of K_I using the formula

$$K_I = IC_{50}/[1 + (K_D/1\ nM)]$$

the dissociation constant K_D is determined with [^{3}H]spiroperidol concentrations between 0.37 and 2.38 nM in three independent experiments.

Acknowledgment. We express our gratitude to M. Kasteleiner and N. Woellmer for their technical assistance and Dr. H.-W. Fehlhaber for NMR and mass spectra.