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Partial dopamine receptor agonists with different degrees of intrinsic activity within a series of 2-(4-aminophenyl)-*N*,*N*-dipropylethylamine derivatives: synthetic chemistry and structure–activity relationships

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Summary — A series of 2-(4-aminophenyl)-*N*,*N*-dipropylethylamine derivatives were synthesized and tested for in vivo intrinsic activity at brain dopamine receptors in the rat. Differences in the sensitivity of dopamine receptors pre- and post-synaptically in the reserpine-treated rat were used to estimate the intrinsic activity of the various compounds as dopamine receptor agonists. Thus, the ability of the compounds to antagonize reserpine-induced increase in neostriatal dopamine synthesis and the suppression of spontaneous locomotor activity were taken as pre-and post-synaptic indices, respectively. The compounds in the present series display a gradient of intrinsic activity depending on the substituents in the aromatic ring. The presence of an amino group or an appropriate acylamino group in the 4-position was found to be critical for the biological activity of these compounds as agonists or antagonists. The introduction of halogen or a trifluoromethyl group in the 3-position resulted in high intrinsic activity (ie, agonist activity). The incorporation of a methyl group in the 3-position or halogens in the 3,5-positions resulted in a gradual decrease in intrinsic activity at rat brain dopamine receptors resulting in a series of compounds ranging from a full agonist to dopamine receptor blockade.

2-(4-aminophenyl)-*N*,*N*-dipropylethylamine derivative /dopamine/ receptor/ intrinsic activity

Introduction

Centrally active partial dopamine (DA) receptor agonists have a pharmacodynamic profile distinct from that of the full agonist and from the DA receptor antagonist. (–)-3-(3-Hydroxyphenyl)-*N*-propylpiperidine (3-PPP) has been a prototype of this group of pharmacological agents [1]. In some animal tests, such as for example antagonism of amphetamine-induced hyperactivity, (–)-3-PPP has the effect of an antagonist [2–4]. Unlike antagonists, however, (–)-3-PPP does not produce extrapyramidal motor dysfunction [5]. Finally, in other tests for dopaminergic receptor mediated functions, like prolactin release, (–)-3-PPP behaves as an agonist and produces a decrease in plasma prolactin levels in acutely hyperprolactinaemic rats [6]. This preclinical pharmacological profile suggests that (–)-3-PPP, and similar compounds could be effective antipsychotic agents with little or no propensity to produce the extrapyramidal or endocrine side effects which are commonly experienced with traditional antipsychotics of the DA-receptor blocking type [7, 8]. Preliminary observations indicate a therapeutic effect in schizophrenia, particularly when associated with negative symptoms, for a few partial DA receptor agonists tested clinically [9–13]. Their general use as antipsychotics may be limited, however, by the fact that most compounds developed and tested to date possess a relatively high degree of intrinsic activity. In order to be effective against positive schizophrenic symptoms as well, the intrinsic activity probably has to be relatively low [14].

In this report we present a new group of compounds with different degrees of in vivo partial DA receptor agonist properties. The objective was to identify DA receptor agonists with an intrinsic activity equal to or less than that displayed by (–)-3-PPP. Thus, the compound should (a) not antagonize reserpine-induced suppression of spontaneous motor activity in rats, whereas it should (b) agonize the reserpine-induced increase in striatal DA synthesis. The reser-

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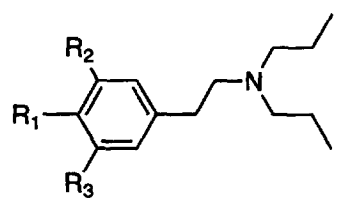
pine-induced depletion of the brain catecholamines results in behavioural suppression that can only be antagonized by postsynaptic DA receptor stimulation by an agonist with intrinsic activity exceeding that of (–)-3-PPP. At the same time, the reserpine-induced DA depletion lifts a tonic suppression of DA synthesis, mediated via inhibitory presynaptic DA autoreceptors [15]. These presynaptic receptors display a higher degree of sensitivity than the postsynaptic receptors and respond also to agonists with less intrinsic activity than (–)-3-PPP [16]. By the operational use of these criteria, we report here a new series of DA receptor agonists presenting a gradient of in vivo intrinsic activity.

Chemistry

Compound **1** in table I was prepared as illustrated in scheme 1. Ethyl cyanoacetate was converted to its anion by potassium hydroxide or potassium carbonate in dimethyl sulfoxide and alkylated in situ with 5-chloro-2-nitro-trifluoromethylbenzene. Selective acid hydrolysis and decarboxylation of the ester group of the obtained ethyl 4-nitro-3-trifluoromethylphenyl-cyanoacetate gave the corresponding 4-nitro-3-trifluoromethylbenzyl cyanide. Selective catalytic hydrogenation of the nitro group in the above cyanide was accomplished under atmospheric pressure and temperature. Conversion of the obtained aniline into the

Table I. 2-(4-Aminophenyl)-*N*,*N*-dipropylethylamine derivatives.



Compound	*4-R_1*	*3-R_2*	*5-R_3*	*Mp (°C)*	*Yield[a] (%)*
1	NH_2	CF_3	H	176–177[b,h] 175–176[c,h]	37[b] 8[c]
2	NH_2	CF_3	H	179–180[g]	74
3	$NHCOCH_3$	H	H	163–164[d,g] 164–165[e]	47[d] 36[e]
4	NH_2	Br	H	213–214[h]	36
5	NH_2	Cl	H	223–225[h]	52
6	NH_2	Cl	H	135–136[g]	90
7	$NHCOCH_3$	Cl	H	170–172[g]	99
8	$NHCOC_6H_5$	Cl	H	141–142[g]	73
9	NH_2	CH_3	H	135–136[j]	26
10	NH_2	Br	Br	184–186[f,g]	24
11	NH_2	Br	Cl	172–173[g]	67
12	NH_2	H	H	234-235[h]	79
13	$NHCOC(CH_3)_3$	Cl	H	145–146[i]	50
14	NH_2	Br	CF_3	134–136[g]	26
15	NHC_2H_5	Cl	H	134–135[i]	21
16	$NHC(=NH)NH_2$	Cl	H	101–102	54
17	$NHCONH_2$	Cl	H	162–164[g]	34
18	$NHSO_2CH_3$	Cl	H	140–142[i]	57

[a]The yields were estimated from the starting material in the multi-step synthesis; [b]*Method I*; [c]*Method II*; [d]*Method III*; [e]*Method IV*; [f]reported [18] mp 184–186 °C; [g]monohydrochloride; [h]dihydrochloride; [i]monooxalate; [j]dioxalate.

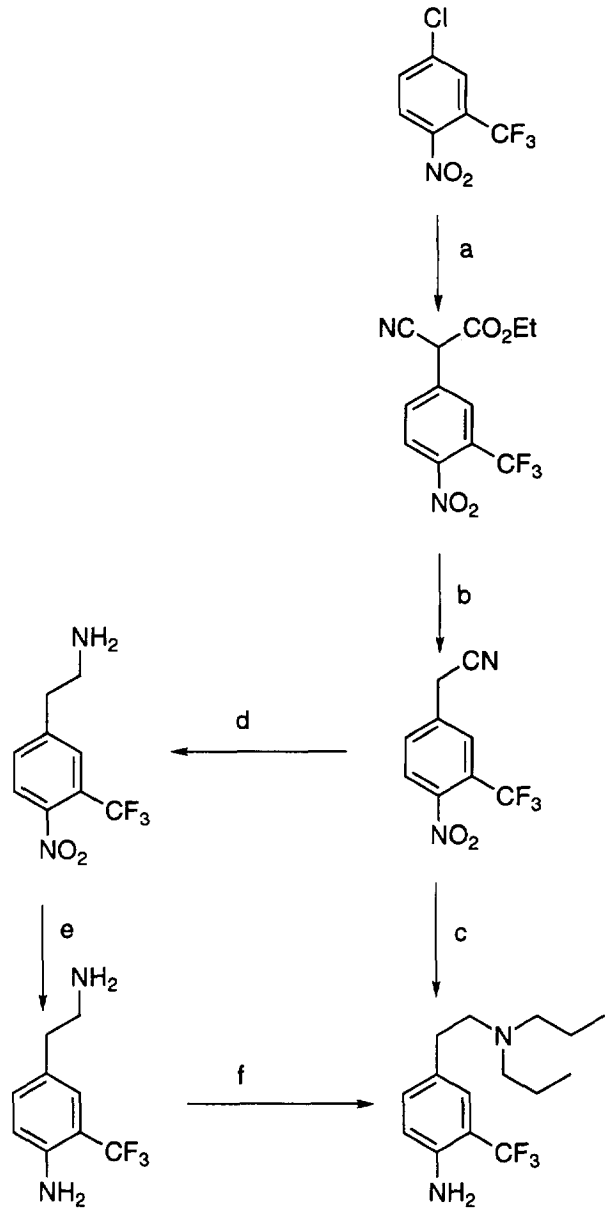
desired amine **1** was then achieved by the admixture of dipropylamine and further hydrogenation at elevated temperature (*Method I*).

Using a different strategy (*Method II*) the cyano group in the above 4-nitro-3-trifluoromethylbenzyl cyanide was first reduced by means of sodium borohydride in the presence of trifluoroacetic acid. The nitro group in the yielded 2-(4-nitro-3-trifluoromethylphenyl)ethylamine was next reduced with catalytically activated hydrogen. Subsequently, dipropylation of the aliphatic amino group of the obtained 2-(4-amino-3-trifluoromethylphenyl)ethylamine with 1-bromopropane, yielded the target amine **1**, which was isolated as the dihydrochloride salt. Preparation of the monohydrochloride **2** from the dihydrochloride **1** was effected by the disproportionation of equivalent amounts of the disalt **1** and free base.

The synthesis of compound **3** started from 2-(4-nitrophenyl)ethyl chloride, which was reacted with dipropylamine. The yielded 2-(4-nitrophenyl)-*N,N*-dipropylethylamine was reduced directly to the corresponding aniline. The reduction was achieved by catalytic hydrogenation (*Method III*) in the presence of palladium or with sodium polysulfide in ethanol (*Method IV*). The intermediate aniline **12** was not isolated at this stage but directly converted into the amide **3**. The preparation of the monochloro compound **5** was effected by treating amide **3** with sulfuryl chloride. The acetyl group was removed with hydrochloric acid and the amine was isolated as the dihydrochloride salt **5**. The monohydrochloride **6** was obtained from **5** by the same procedure used for the preparation of compound **2**. Bromination of amide **3** with bromine in acetic acid and deacetylation of the obtained brominated acetanilide with hydrochloric acid yielded compound **4**. Excessive bromination of the free aniline **4** gave the dibromo derivative **10**. The mixed halogen compounds **11** and **14** were prepared from **5** and **1**, respectively, by bromination under the same conditions used for the preparation of **10**.

Deacetylation of compound **3** yielded the dihydrochloride **12**. The preparation of this compound by reductive amination of 4-aminobenzyl cyanide with dipropylamine, has been described previously [17].

The synthesis of compound **9** started from 3-methylbenzyl cyanide, which was nitrated. Hydrolysis of the obtained 4-nitro-3-methylbenzyl cyanide by hydrochloric acid at elevated temperature and prolonged reaction time yielded 4-nitro-3-methylphenylacetic acid. Transformation of this acid into the acid chloride with thionyl chloride and reaction with dipropylamine gave the corresponding amide, *N,N*-dipropyl-4-nitro-3-methyl-phenylacetamide. Reduction of the amide with lithium aluminium hydride and subsequent reaction of the intermediate 4,4'-bis(2-dipropylaminoethyl)-3,3'-dimethylazobenzene with sodium dithionite gave the desired target amine **9**.



Scheme 1. a: Ethyl cyanoacetate and KOH or K_2CO_3 and dimethyl sulfoxide. b: HCl. c: H_2, Pd and dipropylamine. d: Sodium borohydride and trifluoroacetic acid. e: H_2, Pd. f: Propyl bromide and K_2CO_3 in *N,N*-dimethylformamide.

Acylation of compound **5** with acetic anhydride, benzoyl chloride, pivaloyl chloride and methanesulfonyl chloride, respectively, yielded the amides **7**, **8**, **13** and **18**. Reaction of compound **5** with cyanamide gave

the guanidine **16** and the preparation of the urea derivative **17** was achieved from compound **5** and sodium cyanate. The initial reaction using urea was unsuccessful and necessitated the in situ addition of sodium cyanate and acetic acid.

Finally, the reduction of amide **7** with lithium aluminium hydride yielded the *N*-ethylaniline derivative **15**.

Results and discussion

The reserpine treatment produced a marked, and statistically significant, increase in the DOPA accumulation and a decrease in spontaneous locomotor activity of the rats. The different reference compounds behaved according to expectation (table II). Thus, the DA agonists quinpirole and B-HT 920 both antagonized the reserpine-induced increase in striatal DOPA accumulation and, at least partially, antagonized the reserpine-induced suppression of locomotor activity. The partial DA agonists (–)-3-PPP, EMD 23448 and *trans*-dihydrolisuride were less effective in this regard, whereas bromlisuride, a DA receptor antagonist, did not produce any statistically significant effects. The rank order of the seven compounds, as indicated by the pre- to post-synaptic ratios, is in good agreement with their known in vivo intrinsic activity at brain DA receptors.

On this basis, the present series of compounds have been ranked according to their relative efficacy as DA receptor agonists. Thus, within this series, an amino group or an acylamino group in the 4-position is a necessary condition for biological activity as a DA receptor agonist. One halogen or a trifluoromethyl substituent in position 3 resulted in increased potency compared to the corresponding compounds with two substituents in the 3,5-positions. Furthermore, the halogen compounds were more potent than the corresponding methyl congener. The introduction of a trimethylacetamido group in the 4-position was found to abolish the biological activity **13** (table III).

The affinities of compounds **1**, **6**, **12** and **14** to rat striatal DA D_2 receptors were determined using the DA D_2-selective benzamide radioligand [^{3}H]raclopride (table IV). The 4-amino-substituted **12** displayed low affinity for DA D_2 receptors. However, by introducing a 3-chloro substituent (**5**) the affinity increased more than sevenfold. The introduction of the more electron-withdrawing trifluoromethyl group in the 3-position (**1**) or the introduction of the diortho substituents 3-bromo-5-trifluoromethyl (**14**) further increased the affinity 150- and 400-fold, respectively. The Hill coefficient of **1** and **5** is in general agreement with a higher intrinsic activity compared to **12** and **14** (table IV) and is also in good agreement with the quotients presented in table III. Thus, the disubstitution in the 3- and 5-positions does not appear to be beneficial for agonist activity. This may be due to

Table II. Effects of some reference compounds on striatal DOPA accumulation (nmol g^{-1}) and on locomotor activity (counts min^{-1}) in the rat.

	DOPA (pre-synaptyc index)		*Motor activity (post-synaptic index)*		*Quotient (pre/post)*
Saline controls*	6.3 ± 1.4**		7.8 ± 1.2**		
Reserpine controls*	21.4 ± 4.4		1.7 ± 1.3		
Quinpirole	2.5 ± 0.6**	(125)	5.4 ± 1.7**	(39)	3.2
B-HT 920	2.0 ± 0.3**	(128)	4.0 ± 0.9^{ns}	(62)	2.1
(-)3-PPP	5.1 ± 1.6**	(108)	2.2 ± 0.6^{ns}	(92)	1.2
EMD 23448	4.3 ± 0.9**	(113)	2.0 ± 0.0^{ns}	(95)	1.2
trans-Dihydrolisuride	5.4 ± 0.7**	(106)	2.1 ± 0.4^{ns}	(93)	1.1
Bromlisuride	18.6 ± 1.0^{ns}	(19)	3.3 ± 2.0^{ns}	(74)	0.3
Clenbuterol	20.2 ± 1.3^{ns}	(8)	1.5 ± 1.3^{ns}	(103)	0.1

For doses and schedule of drug injections, see *Experimental protocols*. The table shows means ± SD, based on four observations per experimental group. Statistical evaluation was performed by means of a one-way ANOVA, followed by the Dunnett's *t*-test for comparisons with reserpine-treated controls, as indicated in the table. The pre- and post-synaptic indices are given in parentheses and the quotient in the far right column (see *Experimental protocols*). $^{ns}P > 0.05$; $^{**}P < 0.01$; *pooled values for experiments described in tables II and III.

Table III. Effects of the present series of compounds on DOPA accumulation (nmol g^{-1}) and on locomotor activity (cpm) in the rat.

Compound	*DOPA (pre-synaptic index)*	*Motor activity (post-synaptic index)*	*Quotient (pre/post)*
Saline controls	6.3 ± 1.4**	7.8 ± 1.2**	
Reserpine controls	21.4 ± 4.4	1.7 ± 1.3	
1	3.0 ± 0.5** (122)	3.4 ± 0.3^{ns} (72)	1.7
4	3.4 ± 0.4** (121)	3.4 ± 0.2** (75)	1.6
5	4.1 ± 1.2** (115)	2.0 ± 0.7^{ns} (95)	1.2
7	5.9 ± 1.2** (103)	1.7 ± 0.4^{ns} (100)	1.0
8	8.1 ± 1.6** (88)	2.1 ± 0.5^{ns} (93)	1.0
9	8.8 ± 12.6** (83)	1.7 ± 0.7^{ns} (100)	0 8
10	10.2 ± 0.3** (74)	2.1 ± 0.4* (93)	0.8
11	10.7 ± 2.1** (71)	2.1 ± 0.4^{ns} (107)	0.7
12	15.6 ± 4.9^{ns} (38)	1.6 ± 0.7^{ns} (102)	0.4
13	18.0 ± 2.8^{ns} (23)	2.4 ± 2.1^{ns} (89)	0.3
19a	16.5 ± 1.1^{ns} (32)	1.7 ± 1.0^{ns} (100)	0 3
14	20.0 ± 5.5^{ns} (9)	1.9 ± 0.3^{ns} (97)	0.1
15	21.3 ± 4.7^{ns} (1)	4.0 ± 1.3* (62)	0.0
16	21.0 ± 4.3^{ns} (3)	0.4 ± 0.2** (121)	0.0
17	20.8 ± 1.6^{ns} (4)	1.8 ± 0.4^{ns} (98)	0.0
18	22.4 ± 6.6^{ns} (0)	2.5 ± 0.5^{ns} (87)	0.0

For details see legend to table II. $^{ns}P > 0.05$; $*P < 0.05$; $**P < 0.01$; [a]the *N*-monopropylamine analogue of compound **5.**

interference with a hydrogen-bonding interaction between the amino group and the agonist binding site of the receptor and/or steric interactions with the receptor [19].

Experimental protocols

Chemistry

Melting points were determined in a Mettler FP62 melting point recorder. The elemental analyses were performed by the Department of Analytical Chemistry, University of Lund, Lund, Sweden. Where elemental analyses are indicated by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. The absence of precursors or impurities was examined by GC/MS. The mass spectra were obtained on an ITD800 or an LKB2091 mass spectrometer operating in the CI (CH_4) or EI (70 eV) mode. Gas chromatography was carried out on a HP5890 instrument with a 10 m × 0.1 mm CP-Sil-5 capillary column. ^{1}H NMR spectra were recorded with a Varian A-60A or a Gemini-300 NMR spectrometer. The intermediates were usually not isolated but used directly in the next step.

2-(4-Amino-3-trifluoromethylphenyl)-N,N-dipropylethylamine-dihydrochloride ***1***

Method I. A mixture of 33.9 g (0.3 mol) of ethyl cyanoacetate, 19.2 g of KOH 87.7% (0.3 mol) and 100 mL of dry DMSO was stirred until the KOH dissolved. With external water cooling, 34.0 mL (0.23 mol) of 5-chloro-2-nitrotrifluoromethylbenzene was added at such a rate that the temperature was maintained at about 40 °C. The mixture was stirred for 2 days at room temperature. To the dark-red solution, 60 mL of water, 60 mL of 12 M HCl and 70 mL of acetic acid was added and the mixture was heated under reflux until the evolution of CO_2 ceased after about 45 min. Upon cooling, 1.5 L of water was added and the mixture was then extracted with ether. The extract was washed with water, dried over sodium sulfate and evaporated to give 54.5 g of a pale-yellow oil. The yielded product (54.5 g) was dissolved in 300 mL of anhydrous ethanol and hydrogenated with H_2/Pd (10% on charcoal) at atmosphe-

Table IV. Potencies of selected compounds to inhibit [^{3}H]raclopride binding to rat striatal DA D_2 receptors.

Compound	K_i *(nM)*	n_H
1	15.9 ± 0.50	0.58 ± 0.07
5	321 ± 85	0.59 ± 0.07
12	2380 ± 280	0.82 ± 0.03
14	5.70 ± 1.0	0.78 ± 0

The results are means ± SEM of two independent experiments. n_H = Hill coefficient.

ric pressure and room temperature until the volume of hydrogen (15 L) corresponding to the reduction of the nitro group had been absorbed (about 2 h). The apparatus was flushed with nitrogen, 100 mL of dipropylamine and an additional amount of catalyst was added. The hydrogenation was continued at about 50 °C and atmospheric pressure. The absorption of hydrogen was slow and ceased when 6.5 L of hydrogen had been absorbed (about 8 h). The catalyst was filtered off and washed with ethanol. The filtrate was concentrated under reduced pressure and to the residual oil 800 mL of dilute HCl was added. The mixture was washed with ether, alkalized with NaOH and extracted with ether. The extract was dried over Na_2SO_4 in the presence of activated carbon. The ether was evaporated and the pale-yellow oil obtained (40.9 g) was dissolved in 200 mL ether and acidified with HCl in ether. The precipitated dihydrochloride was filtered off and recrystallized from ethanol/diisopropyl ether to give 30.4 g of the salt, mp 176–177 °C. ^{1}H NMR (D_2O) δ 7.8 (s, 1H, Ar), 7.6 (d, 1H, Ar), 7.4 (d, 1H, Ar), 3.5–3.1 (m, 8H, $4CH_2$), 1.8–1.6 (m, 4H, $2CH_2$), 0.9 (t, 6H, $2CH_3$); CIMS *m/z* 289 ($M + H^+$). Anal $C_{15}H_{23}F_3N_2$·2HCl (C, H, Cl, F, N).

Method II. A mixture of 22.6 g (0.2 mol) of ethyl cyanoacetate, 35.0 g (0.25 mol) of K_2CO_3, a catalytic amount of KI and 22.5 mL (0.15 mol) of 5-chloro-2-nitrotrifluoromethylbenzene in 60.0 mL of DMF was stirred and heated at 100 °C for 12 h. To the dark-red solution 500 mL of water was added and the mixture was made acidic by dropwise addition of 12 M HCl while cooling and stirring. The mixture was extracted with ether and the extract was washed with water, dried (Na_2SO_4) and the organic layer concentrated under reduced pressure. To the residue, 39.6 g of a yellow oil, was added 150 mL of water, 50 mL of acetic acid and 20 mL of concentrated HCl and the mixture was heated under reflux until the evolution of CO_2 ceased after about 45 min. Upon cooling 500 mL of water was added and the mixture was then extracted with ether. The extract was dried (Na_2SO_4) and the solvent evaporated to give 38.0 g of crude 4-nitro-3-trifluoromethylbenzyl cyanide. To a stirred suspension of 16.3 g of $NaBH_4$ in 150 mL THF, 32 mL trifluoroacetic acid in 50 mL THF was added over a period of 10 min at 20 °C. To this solution was added 24.4 g of the above-mentioned crude nitrile dissolved in 50 mL THF. After 12 h at room temperature the reaction mixture was concentrated to dryness in vacuo and excess reagent was decomposed with 500 mL of ice-water, alkalized with KOH and extracted with ether. The organic layer was extracted with dilute HCl. The acid solution was alkalized and again extracted with ether. The ether extract was dried (Na_2SO_4) and the solvent evaporated to give 11.2 g of crude of 2-(4-nitro-3-trifluoromethylphenyl)ethylamine. The product was dissolved in 200 mL of dilute HCl and hydrogenated over 5% Pd on charcoal at about 50 °C and atmospheric pressure. The catalyst was filtered off and the filtrate was alkalized and extracted with ether. The extract was dried (Na_2SO_4) and the solvent evaporated to give a residue of 7.4 g of crude 2-(4-amino-3-trifluoromethylphenyl)ethylamine. The oily compound was dissolved in 50 mL of DMF and 14.0 g of K_2CO_3, a catalytic amount of KI and 9.0 mL of 1-bromopropane were added. The mixture was heated at 100 °C under stirring for 2 h and was then diluted with 800 mL of water and extracted with ether. The ether layer was separated, extracted with dilute HCl, alkalized and again extracted with ether. The extract was dried with Na_2SO_4 and NaOH in the presence of activated carbon and acidified with HCl in ether. The precipitated dihydrochloride was filtered off and recrystallized from ethanol/diisopropyl ether to give 5.7 g of the salt, mp 173–175 °C. A second recrystallization from ethanol/ethyl acetate gave 4.2 g of an analytically pure sample, mp 175–176 °C.

2-(4-Amino-3-trifluoromethylphenyl)-N,N-dipropylethylamine monohydrochloride ***2***

2-(4-Amino-3-trifluoromethylphenyl)-*N,N*-dipropylethylamine dihydrochloride (3.6 g, 0.01 mol) was dissolved in 15 mL of water and alkalized with NaOH. The base was extracted with ether, dried with Na_2SO_4 and NaOH and the ether was evaporated. The yielded base (2.77 g, 0.0096 mol) was dissolved in 25 mL of ethanol and the solution was added to 3.4 g (0.0094 mol) of the corresponding dihydrochloride dissolved in 25 mL of ethanol. After the addition of 400 mL of ether and cooling, the precipitated monohydrochloride was filtered off and washed with ether. Yield: 4.8 g, mp 179–180 °C. Anal $C_{15}H_{23}F_3N_2$·HCl (Cl).

2-(4-Acetamidophenyl)-N,N-dipropylethylamine hydrochloride ***3***

Method III. A mixture of 90.0 g (0.48 mol) of 4-nitrophenethylchloride, 170 mL (1.24 mol) of dipropylamine and 10.0 g of KI in 250 mL of ethanol was heated under reflux for 30 h. The solvent was evaporated at reduced pressure. The residue was treated with dilute HCl and extracted with ether. The water layer was made basic with NaOH and extracted with ether. The extract was washed with water and dried with Na_2SO_4. The solvent was evaporated and the residue, 107.5 g of an oil, was dissolved in dilute HCl and hydrogenated with H_2/Pd (5%) at atmospheric pressure and about 50 °C. When the hydrogen uptake had ceased, the catalyst was filtered off and the filtrate was made basic with NaOH and extracted with ether. The extract was dried with Na_2SO_4 and the solvent was evaporated. To the residue, 98.8 g of an oil, 75 mL of acetic anhydride was added while stirring. The mixture was heated under reflux for 10 min and gradually diluted with water to a volume of 1 L. The solution was made basic with NaOH and extracted with ether. The extract was dried with Na_2SO_4 and treated with dry HCl in ether. The precipitate was recrystallized from ethyl acetate/ethanol. Yield 67.3 g, mp 163–164 °C: ^{1}H NMR (D_2O) δ 7.4 (d, 4H, Ar), 3.4–2.9 (m, 8H, $4CH_2$), 2.1 (s, 3H, CH_3), 1.8–1.4 (m, 4H, $2CH_2$), 0.9 (t, 6H, $2CH_3$). Anal $C_{16}H_{26}N_2O$·HCl (C, H, Cl, N, O).

Method IV. A mixture of 131.0 g (0.7 mol) of 4-nitrophenethylchloride, 245 mL (1.8 mol) of dipropylamine and 10 g of KI in 350 mL of ethanol was heated under reflux for 30 h. The solvent was evaporated at reduced pressure and the residue was treated with dilute HCl and extracted with ether. The water layer was made basic with NaOH and extracted with ether. The extract was washed with water and dried with Na_2SO_4. The solvent was evaporated and the residue, 170 g of an oil, was dissolved in 100 mL of ethanol and added dropwise while stirring to a refluxing solution of 336.0 g Na_2S·$9H_2O$ and 44.8 g S in 700 mL of water and 350 mL of ethanol. The mixture was heated under reflux for 4 h. The ethanol was evaporated and the residue was extracted with ether. The extract was dried with Na_2SO_4 in the presence of decolorizing carbon and the solvent was evaporated under reduced pressure. To the residue, 134.0 g of an oil, 120 mL of acetic anhydride was added while stirring. The mixture was heated under reflux for 10 min and concentrated to half its volume. To the residue 800 mL of water was added dropwise under stirring. The solution was made basic with NaOH and extracted with ether. The extract was dried with Na_2SO_4 in the presence of decolorizing carbon and treated with dry HCl in ether. The precipitate was recrystallized from ethyl acetate/ethanol. Yield 74.8 g, mp 164–165 °C.

2-(4-Amino-3-bromophenyl)-N,N-dipropylethylamine dihydrochloride ***4***

To a stirred solution of 22.6 g (0.075 mol) of compound **3** in 400 mL of HAc was added 6.0 mL (0.12 mol) of Br_2. The mixture was stirred at room temperature for 3 days and at about 100 °C for 3 h. The solvent was evaporated and the residue was dissolved in 100 mL of concentrated HCl and 75 mL of water. The solution was heated under reflux for 4 h and the main part of the acid was evaporated. To the residue was added water and the solution was made basic with NaOH and extracted with ether. The extract was dried with Na_2SO_4 in the presence of decolorizing carbon and treated with dry HCl in ether. The precipitate was filtered off, dissolved in water and made basic with NaOH. The amine was extracted with ether, purified by HPLC and transformed into the dihydrochloride salt by means of HCl in ether. Yield 10.0 g, mp 213–214 °C: ^{1}H NMR (D_2O) δ 7.6 (s, 1H, Ar), 7.3 (d, 2H, Ar), 3.2–2.8 (m, 8H, $4CH_2$), 1.8–1.2 (m, 4H, $2CH_2$), 0.7 (t, 6H, $2CH_3$). Anal $C_{14}H_{23}BrN_2 \cdot 2HCl$ (Cl); calc 19.05, found 19.6.

2-(4-Amino-3-chlorophenyl)-N,N-dipropylethylaminedihydrochloride ***5***

A solution of 131.0 g (0.7 mol) of 2-(4-nitrophenyl)ethyl chloride, 245.0 mL of dipropylamine (1.8 mol) and 10.0 g of KI in 350.0 mL of ethanol was refluxed for 30 h. The solvent was evaporated and the residue is treated with 2 L of diluted HCl, washed with ether, alkalized with NaOH and extracted with ether. The extract was evaporated and the residual oil was dissolved in 100 mL of ethanol and the solution was added in portions to a solution of 48.0 g of sulfur and 362.0 g of $Na_2S \cdot 9H_2O$ in 700 mL of water and 350 mL of ethanol. The mixture was refluxed for 5 h, the ethanol was evaporated and 2 L of water was added and the mixture was extracted with ether. The extract was dried (Na_2SO_4) and solvent evaporated. To the yielded residue, 122.1 g of an oil, 110 mL of acetic anhydride was added in portions and the mixture was refluxed for 5 min. Water was added dropwise under stirring, the mixture was alkalized with NaOH and extracted with ether. The extract was dried (Na_2SO_4) and acidified with HCl in ether. The yielded brown syrupy liquid was dissolved in 500 mL of chloroform and 88.0 mL (1.1 mol) of sulfuryl chloride was added dropwise under stirring. After the addition, the mixture was refluxed for 2 h. The solvent was evaporated and the residue was dissolved in 200 mL of water and 250 mL of concentrated HCl and the solution was refluxed for 5 h. The main part of the HCl was evaporated and 1 L of water was added and the mixture was filtered. The filtrate was alkalized, extracted with ether and dried (Na_2SO_4) in the presence of activated carbon. After evaporation of the solvent the filtrate gave 138.3 g of a brown oil. The product was dissolved in 500 mL of ethanol and 100 mL of concentrated HCl was added in portions. The solvents were evaporated and the residue was dissolved in 500 mL of hot 95% ethanol. A small amount of insoluble matter was removed by filtration and to the hot filtrate was added ethyl acetate. After cooling in an ice-bath, the mixture was filtered and the precipitate was washed with ether to give 118.3 g of the dihydrochloride salt, melting at 223–225 °C: ^{1}H NMR (D_2O) δ 7.6 (s, 1H, Ar), 7.4 (s, 2H, Ar), 3.4–2.8 (m, 8H, $4CH_2$), 1.8–1.2 (m, 4H, $2CH_2$), 0.8 (t, 6H, $2CH_3$). Anal $C_{14}H_{23}ClN_2 \cdot 2HCl$ (C, H, Cl, N); C: calc 51.31, found 50.2.

2-(4-Amino-3-chlorophenyl)-N,N-dipropylethylamine monohydrochloride ***6***

Dihydrochloride **5** (11.8 g, 0.036 mol) was dissolved in 110 mL of ethanol and added under stirring to 9.5 g (0.037 mol) of the corresponding base. The monosalt was precipitated with ether and filtered off. Yield 19.0 g (90%), mp 135–136 °C. Anal $C_{14}H_{23}ClN_2 \cdot HCl$ (C, H, Cl, N).

2-(4-Amino-3,5-dibromophenyl)-N,N-dipropylethylamine hydrochloride ***10***

To a stirred solution of 4.6 g (0.012 mol) of compound **4** in 200 mL of acetic acid was added 0.8 mL (0.016 mol) of bromine. The mixture was stirred at room temperature overnight. The solvent was evaporated and the residue was made basic with 2 M NaOH and extracted with ether. The extract was dried with Na_2SO_4 and treated with dry HCl in ether. The precipitate was filtered and recrystallized twice from ethanol/ether. Yield 1.2 g, mp 184–186 °C. ^{1}H NMR (D_2O) δ 7.5 (s, 2H, Ar), 3.4–2.9 (m, 8H, $4CH_2$), 1.8–1.6 (m, 4H, $2CH_2$), 0.9 (t, 6H, $2CH_3$). Anal $C_{14}H_{22}Br_2N_2 \cdot HCl$ (Cl).

2-(4-Aminophenyl)-N,N-dipropylethylamine dihydrochloride ***12***

A stirred solution of 29.8 g (0.1 mol) of compound **3** in 50 mL water and 100 mL of 12 M HCl was refluxed for 3 h and the solvent evaporated. The residue was recrystallized from ethanol/diisopropyl ether. Yield 23.2 g, mp 234–235 °C. Anal $C_{14}H_{24}N_2 \cdot 2HCl$ (C, H, Cl, N).

2-(4-Amino-3-bromo-5-chlorophenyl)-N,N-dipropylethylamine hydrochloride ***11***

Compound **5** (4.9 g, 0.015 mol) was dissolved in 200 mL of acetic acid and a sufficient amount of water to get the salt into solution. A solution of 1.0 mL of bromine in 50 mL of acetic acid was added and the mixture was left for 1 h at room temperature. The solvent was evaporated and the residue was alkalized with 2 M NaOH and extracted with ether. The extract was dried with Na_2SO_4 and treated with dry HCl in ether. The precipitate was filtered off and recrystallized from ethanol/ether. Yield 3.7 g, mp 172–173 °C. Anal $C_{14}H_{22}BrClN_2 \cdot HCl$ (C, H, Cl, N), C calc 45.3, found 44.3.

2-(4-Amino-3-bromo-5-trifluoromethylphenyl)-N,N-dipropylethylaminehydrochloride ***14***

Hydrochloride **14** was prepared similarly to compound **11**, from 1.4 g (0.0038 mol) of compound **1** and 0.2 mL (0.0042 mol) of bromine. Yield 0.4 g, mp 134–136 °C. CIMS *m/z* 368 ($M + H^+$).

3-Methyl-4-nitrophenylacetic acid

To a mixture of 45.0 mL of 65% nitric acid and 45.0 mL of concentrated H_2SO_4, 15.0 g of 3-methylbenzyl cyanide was added dropwise under stirring and cooling in ice. The mixture was stirred for 1 h at room temperature and then poured on ice and extracted with CH_2Cl_2. The extract was washed with water and dried over Na_2SO_4. The solvent was evaporated and the residue, 19.1 g of an oil, was dissolved in 100 mL of concentrated HCl, 75 mL of water and sufficient acetic acid to get the cyanide into solution. The mixture was refluxed for 6 h, diluted with water and cooled in ice. The formed precipitate, 12.6 g, yielded after recrystallization three times from HAc/water, 5.8 g of the pure acid, melting at 105–106 °C. Anal $C_9H_9NO_4$ (C, H, N).

2-(4-Amino-3-methylphenyl)-N,N-dipropylethylamine dioxalate ***9***

To a solution of 9.2 g (0.047 mol) of 3-methyl-4-nitrophenylacetic acid in 100 mL of $CHCl_3$ was added 20 mL of $SOCl_2$. The mixture was heated at reflux for 1 h, the solvent was evaporated and to the residue was added 25 mL of dipropylamine in 100 mL of $CHCl_3$ in portions. After 1 h at room temperature the solvent was evaporated and 200 mL of water

was added. The yielded amide was extracted with ether, dried with Na_2SO_4 and the solvent was evaporated. The residue, 13.0 g of an oil, was dissolved in 100 mL of dry ether and the solution was added dropwise under stirring to 10.0 g of $LiAlH_4$ in 100 mL of dry ether. The mixture was refluxed overnight and 30 mL of a saturated solution of Na_2SO_4 was added dropwise while cooling and stirring. After filtration the filtrate was dried with Na_2SO_4 and the solvent was evaporated. The residue, 10.9 g of a red oil, was dissolved in 100 mL of ethanol and water was added until a weak turbidity was observed. To the mixture 25.0 g of $Na_2S_2O_4$ was added in portions and the solution was heated at 50 °C for 2 h and left overnight at room temperature. The scarlet color changed gradually into faint yellow. The ethanol was evaporated and to the residue was added 2 M NaOH solution to the double volume and the mixture was extracted with ether. The extract was dried with Na_2SO_4 and evaporated. The residual oil, 5.4 g, was dissolved in 100 mL of ethanol and added to a solution at 10.0 g of $(COOH)_2 \cdot 2H_2O$ in 50 mL of THF. After cooling overnight, the obtained precipitate was filtered off. Recrystallization from ethanol gave 5.1 g of an analytical pure sample of the dioxalate, melting at 135–136 °C. EIMS *m/z* 234 (M^+). Anal $C_{15}H_{26}N_2 \cdot (COOH)_2$ (C, H, N).

2-(4-Acetamido-3-chlorophenyl)-N,N-dipropylethylamine hydrochloride **7**

To a solution of 2.0 g (0.006 mol) of compound **5** in 25 mL of HAc was added 10.0 mL of Ac_2O. The mixture was heated for 0.5 h and 500 mL of ether was added. The yielded semi-solid precipitate was filtered off and stirred with cool ethyl acetate. The obtained crystalline salt was filtered off and washed with ether. Yield 1.3 g, mp 170–172 °C. ^1H NMR (D_2O) δ 7.5–7.2 (m, 3H, Ar), 3.4–3.0 (m, 8H, $4CH_2$), 2.2 (s, 3H, CH_3), 1.8–1.6 (m, 4H, $2CH_2$), 0.9 (t, 6H, $2CH_3$). Anal $C_{16}H_{25}ClN_2O \cdot HCl$ (C, H, N).

2-(4-Benzamido-3-chlorophenyl)-N,N-dipropylethylamine hydrochloride **8**

To a mixture of 6.5 g (0.02 mol) of compound **5** and 4.0 g (0.1 mol) of NaOH in 200 mL of water was added while cooling and stirring 5.0 mL of benzoyl chloride. After 2 h the yielded precipitate was extracted with ether and dried with Na_2SO_4. The extract was treated with dry HCl and the precipitated salt was recrystallized from ethanol/ether. Yield 5.8 g, mp 141–142 °C: CIMS *m/z* 360 ($M + H^+$). Anal $C_{21}H_{27}ClN_2O \cdot HCl$ (C, H, Cl, N); C: calc 63.79, found 62.6. Cl: calc 17.93, found 18.7.

2-(4-Trimethylacetamido-3-chlorophenyl)-N,N-dipropylethylamine oxalate **13**

To a solution of 6.5 g (0.02 mol) of compound **5** in 50 mL of dry pyridine was added 5.0 mL (0.04 mol) of trimethylacetyl chloride. The mixture was stirred overnight at room temperature and heated at about 100 °C for 1 h. Water was added to a volume of 1 L and the mixture was alkalized with NaOH and extracted with ether. The extract was washed with water and extracted with dilute HCl. The acid layer was alkalized with NaOH and again extracted with ether. The extract was dried with Na_2SO_4 and the solvent was evaporated. The residue was dissolved in 25 mL of ethanol and 1.5 g (0.12 mol) of $(COOH)_2 \cdot 2H_2O$ in 25 mL of ethanol was added. The solution was diluted with ether until a weak turbidity arose. After cooling overnight the salt was filtered off and washed with THF and ether. Yield 4.3 g, mp 145–146 °C. EIMS *m/z* 338 (M^+). Anal $C_{19}H_{31}ClN_2O \cdot (COOH)_2$ (C, H, Cl, N).

2-(3-Chloro-4-methanesulfonamidophenyl)-N,N-dipropylethylamine oxalate **18**

To 6.5 g (0.02 mol) of compound **5** in 20 mL of pyridine was added 2.8 g (0.01 mol) of K_2CO_3 and while cooling in ice 2.5 mL (0.03 mol) of CH_3SO_2Cl. The mixture was stirred overnight at room temperature and diluted with water to 500 mL. The pH-value was adjusted to 8 by the addition of concentrated NH_4OH and the mixture was extracted with ether. The extract was dried with Na_2SO_4 and the solvent was evaporated; 5.8 g (0.017 mol) of the residual oil (7.5 g) was dissolved in 50 mL of acetone and 2.52 g (0.02 mol) of $(COOH)_2 \cdot 2H_2O$ in 50 mL of acetone was added. The solution was diluted with ether until turbidity and cooled overnight. The yielded precipitate was filtered off and washed with acetone and ether. Yield 4.8 g, mp 140–142 °C. EIMS *m/z* 332 (M^+). ^1H NMR (D_2O) δ 7.6–7.3 (m, 3H, Ar), 3.4–2.9 (m, 11 H, CH_3, $4CH_2$), 1.7–1.4 (m, 4H, $2CH_2$), 0.9 (t, 6H, $2CH_3$). Anal $C_{15}H_{25}ClN_2O_2S$ $(COOH)_2$ (C, H, Cl, N, S); Cl: calc 8.38, found 7.6.

2-(3-Chloro-4-guanidinophenyl)-N,N-dipropylethylamine **16**

A mixture of 13.0 g (0.04 mol) of compound **5** and 4.5 g of H_2NCN in 30 mL of water was acidified by the addition of an excess of concentrated HCl. The mixture was refluxed overnight, diluted with an equal volume of water, alkalized with NaOH and extracted with ether. The extract was dried over Na_2SO_4 and NaOH and the solvent was evaporated. The residual oil solidified gradually upon standing. The obtained product was stirred into petroleum ether and filtered off. Yield 6.4 g, mp 101–102 °C. EIMS *m/z* 296 (M^+). ^1H NMR ($CDCl_3$) δ 7.3–6.8 (m, 3H, Ar), 2.7–2.3 (m, 8H, $4CH_2$), 1.4 (dd, 4H, $2CH_2$), 0.8 (t, 6H, $2CH_3$). Anal $C_{15}H_{25}ClN_4$ (C, H, Cl, N); C: calc 60.69, found 59.8.

2-(3-Chloro-4-ureidophenyl)-N,N-dipropylethylamine hydrochloride **17**

A mixture of 13.0 g (0.04 mol) of compound **5**, 25 mL of water and 25.0 g of H_2NCONH_2, in 40 mL of concentrated HCl was refluxed under stirring overnight. To the solution was added NaOCN by portions until the solution turned alkaline and the mixture was homogenized with HAc and refluxed for 1 h. After the addition of NaOH the mixture was extracted with ether. The extract was washed with water and the solvent was evaporated. The residue (10.6 g) was purified by HPLC and the product (8.0 g) was dissolved in ether and the hydrochloride salt was precipitated by the addition of HCl in ether. The product was recrystallized from ethyl acetate/ethanol. Yield 4.5 g, mp 162–164 °C. EIMS *m/z* 297 (M^+). Anal $C_{15}H_{24}ClN_3O \cdot HCl$ (C, H, Cl, N); Cl: calc 21.21, found 20.6.

2-(3-Chloro-4-ethylaminophenyl)-N,N-dipropylethylamino oxalate **15**

A solution of 3.1 g (0.09 mol) of compound **7** in 50 mL of water was alkalized with NaOH and extracted with ether. The extract was dried (Na_2SO_4) and the ether evaporated. The residue was dissolved in 50 mL of dry Et_2O and 2.0 g of $LiAlH_4$ added by portions. The mixture was stirred and heated under reflux for 2 h. After dropwise addition of 6.0 mL of saturated Na_2SO_4 solution the mixture was filtered. The filtrate was collected, dried with Na_2SO_4 and the ether was evaporated. The residual oil was dissolved in 50.0 mL of ethanol and added to a solution of 2.6 g of $(COOH)_2 \cdot 2H_2O$ in 25.0 mL of ethanol. The oxalate salt was precipitated by the addition of ether and the crude product was recrystallized twice from ethanol/ether. Yield 0.7 g, mp 134–135 °C. EIMS *m/z* 282 (M^+). Anal $C_{16}H_{27}ClN_2 \cdot (COOH)_2$ (C, H, Cl, N).

Pharmacology

Animals
Adult male Sprague–Dawley rats (280–320 g) (ALAB Laboratorietjänst AB, Sollentuna, Sweden) were used. The animals arrived in the laboratory at least 10 days before being used in experiments, and were housed under controlled conditions of relative humidity (55–65%) temperature (21 °C) and light–dark cycle (12:12 h, lights off at 0600 h). Food (R36, Ewos, Södertälje, Sweden) and tap water were freely available in the home cage.

Open-field motor activity
The rats were observed in a square open-field arena (680 × 680 × 450 mm), equipped with two rows of photocells, sensitive to infrared light, placed 40 and 125 mm above the floor, respectively. The photocells were spaced 90 mm apart and the last photocell in a row was spaced 25 mm from the wall. The open-field arena was enclosed in a ventilated, sound-attenuating box with a perspex top. Measurements were made in the dark and performed between 0900–1600 h.

Interruption of photocell beams were collected by means of a microcomputer. *Locomotor activity* and *Rearing* were defined as all interruptions of photobeams in the lower and upper rows, respectively. For further details, see Ahlenius and Hillegaart [5].

Biochemistry
The animals were decapitated by means of a guillotine and the brain, including the olfactory bulb rostrally and the medulla oblongata caudally, was quickly removed. The brain was placed in a mould where it could be sliced into 2.5 mm sections by a thin stainless steel wire (Ø = 70 μm). The dorsal neostriatum was dissected on ice from one of these slices. The rostral edge of the slice was approximately + 2.1 mm in relation to bregma. The brain was cut at an inclination of approximately 7°, such that ventrally the sections extended slightly rostrally, according to the horizontal plane in the atlas of Paxinos and Watson [20]. The approximate mean weight of these neostriatal samples was 50 mg. The samples were immediately frozen on dry ice and stored at −70 °C until processing. Dihydroxyphenylalanine (DOPA) and 5-hydroxytryptophan (5-HTP) were determined by means of coupled column liquid chromatography with electrochemical detection. The preparation of the samples and further details are given in Magnusson et al [21] and Mohringe et al [22].

Experimental procedures
The animals were pretreated with reserpine (Fluka, Buchs, Switzerland), 5 mg kg^{-1} SC, 18 h before administration of the test compound in a standard dose of 30 μmol kg^{-1} sc. Five minutes following administration of the test compound, the animals were placed in the open-field arena and the spontaneous motor activity was recorded for 30 min, as described above. At the end of the open-field session, all animals received the inhibitor of cerebral aromatic L-amino acid decarboxylase 3-hydroxybenzylhydrazine 2HCl (NSD-1015) (Sigma, Saint Louis, MO), 100 mg kg^{-1} ip, and were returned to their home-cage until decapitation 30 min later. Reserpine was dissolved in a minimal quantity of glacial acetic acid and made up to volume in 5.5% glucose. NSD-1015, and the test compounds, were dissolved in physiological saline. Where appropriate, controls received the corresponding vehicle. The injected volume was in all cases 2 mL kg^{-1}.

Selection criteria
The index for post-synaptic DA receptor stimulation was defined as the antagonism of reserpine-induced suppression of locomotor activity. The decrease in activity produced by reserpine, as compared to vehicle-treated controls, was defined as 100 per cent. The corresponding index for pre-synaptic activity was defined as the per cent decrease in DA synthesis in the reserpine-treated animals, where a 100 per cent decrease by the test compound, corresponds to the synthesis of vehicle-treated controls. Thus, a DA agonist with preference for autoreceptors should not antagonize the reserpine-induced suppression of locomotor activity, ie, a post-synaptic index of 100. At the same time there should be an antagonism of the reserpine-induced increase in brain DA synthesis. If the DOPA values were brought back to control level, the pre-synaptic index should also be 100. The quotient pre- to post-synaptic activity is in this case 1.00. The quotient was thus calculated as follows:

$$(LMA_C - LMA_T)(LMA_C - LMA_R)^{-1}\ [(DOPA_R - DOPA_T)(DOPA_R - DOPA_C)^{-1}]^{-1}$$

where LMA = locomotor activity; C = vehicle controls; T = test compound; and R = reserpine.

[^{3}H]Raclopride binding assays
Rat striatal membranes were prepared as described previously [23]. In brief, the rats were decapitated and the striata were dissected on ice. The tissues were homogenized in 0.05 M Tris-HCl and washed by centrifugation. The final pellet was homogenized and suspended in 0.32 M sucrose and stored at −70 °C. On the day of the experiment, the membranes were thawed and suspended in the following assay buffer (in mM): 50 Tris-HCl, 120 NaCl, 5 KCl, 1 $MgCl_2$, 0.1 EDTA, 0.01 pargyline and 0.01% ascorbic acid; pH 7.6 to a final concentration of 2.5 mg original wet weight/0.5 mL. The membranes were preincubated for 10 min at 37 °C.

The competition studies with [^{3}H]raclopride (2 nM) and appropriate test compound (10–12 concentrations) were performed in duplicate at 30 °C for 60 min. Nonspecific binding was defined with 1 μM (+)-butaclamol. The incubations were terminated by rapid filtration throught Whatman GF/B glas fiber filters and subsequent washing with cold buffer (50 mM Tris-HCl, pH 7.4) using a Brandel cell harvester. Scintillation cocktail was added and the radioactivity determined in a Packard 2500TR liquid scintillation counter at about 50% efficiency. The data were analysed by nonlinear regression using the LIGAND program [24]. The K_d value (1.15 nM) obtained from saturation studies were used to calculate the K_i values by the LIGAND program. The Hill coefficients were calculated for each individual experiment.

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