Thiazoloindans and Thiazolobenzopyrans: A Novel Class of Orally Active Central Dopamine (Partial) Agonists

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The 2-aminothiazole moiety has proven its value in medicinal chemistry as a stable and lipophilic bioisosteric replacement of a phenol group. This approach has provided dopamine (DA) agonists with good oral availability. To further explore its use in the development of DA agonists, we have combined the 2-aminothiazole moiety with 2-aminoindans and 3-aminobenzopyrans, which are known templates for DA agonists. In this study we have synthesized 6-amino-3-(*N*,*N*-di-*n*-propylamino)-3,4-dihydro-2*H*-thiazolo[5,4-*f*]-[1]benzopyran (**12**) and 6-amino-2-(*N*,*N*-di-*n*-propylamino)thiazolo[4,5-*f*]indan (**20**) and several analogues (**13**, **17**, and **21**). The affinity of the thiazolobenzopyrans and thiazoloindans for DA receptors was evaluated, which revealed compound **20** to have high affinity for DA D_3 receptors. In addition, the compounds were screened for their potential to inhibit lipid peroxidation, to determine their radical scavenging properties. Compounds **12**, **20**, and **21** were subjected to further pharmacological evaluation in a functional assay to determine intrinsic activity. Compound **20** was also studied with microdialysis (to determine effects on DA turnover in striatum) and in unilaterally 6-OH-DA lesioned rats (to determine their potential as DA agonists). These studies selected compound **20** (GMC 1111) as particularly interesting. Compound **20** caused a rotation activation in unilaterally 6-OH-DA lesioned rats and an increase in DA turnover in rat striatum. This dual agonist/antagonist action is best accounted for by its partial agonism at striatal DA D_2 receptors. Interestingly, **20** displayed long-lasting activity and excellent oral availability in 6-OH-DA lesioned rats, making this compound potentially useful for the treatment of Parkinson's disease.

Introduction

Parkinson's disease (PD) is a neurodegenerative disease of the substantia nigra, causing a dopamine (DA) deficiency in the striatum, which in turn causes movement disorders (rigidity, hypokinesia). Probably, this degeneration of neurons is inflicted by reactive oxygen(-derived) free radicals.[1,2] Restoring nigrostriatal DA neurotransmission by administration of L-DOPA, possibly with the coadministration of DA agonists, is still the dominant therapy for PD. This therapy relieves the symptoms but does not cure PD. Paradoxically, it has been suggested that the prooxidant properties of L-DOPA may contribute to the progression of the disease.[3] Therefore, new approaches for the treatment of PD are needed. New DA agonists for the treatment of PD should not display prooxidant activity like L-DOPA, but preferably antioxidant activity.[4,5]

The 2-aminothiazole functionality has been successfully applied as a heterocyclic bioisostere of the phenol moiety in DA agonists such as talipexole (**1**; Chart 1), a DA agonist with some selectivity for the DA autoreceptor,[6] PD 118440 (**2**), a DA autoreceptor agonist,[7] and pramipexole (**3**), a DA agonist with preference for the DA D_3 (over DA D_2) receptor.[8,9] In these compounds, the amino group on the 2-aminothiazole moiety effectively replaces the hydroxy group of a phenol (or catechol) moiety, to form a presumed hydrogen bond with the receptor binding site. Compared to a phenol group, a 2-aminothiazole moiety is more lipophilic and displays improved oral availability.[7] In addition, some compounds with a 2-aminothiazole moiety were found to

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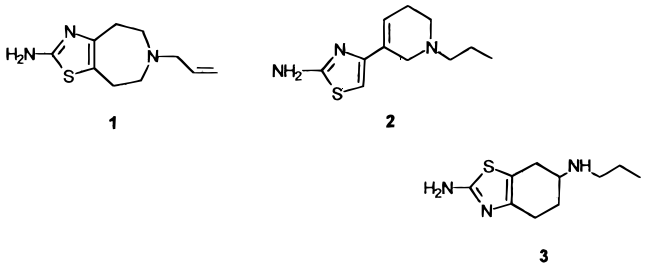
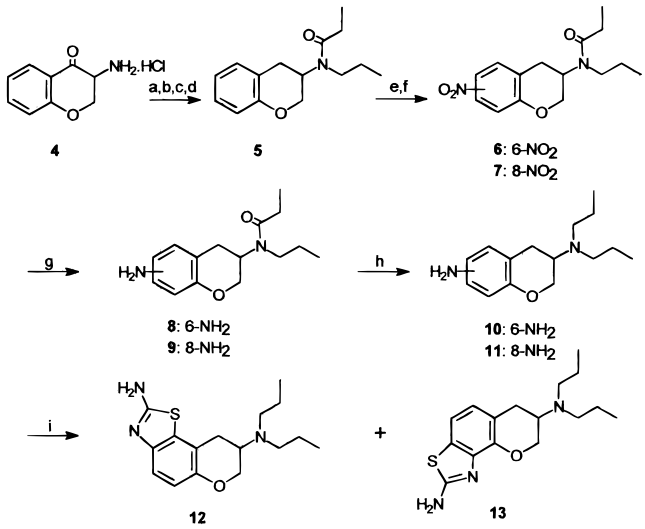
Chart 1. Chemical Structures of DA Agonists with 2-Aminothiazole Functionality: Talipexole (**1**), PD 118440 (**2**), and Pramipexole (**3**)



Scheme 1[a]



[a] Reagents: (a) propionyl chloride, Et_3N, CH_2Cl_2, 0 °C; (b) 10% Pd/C, H_2, EtOH; (c) $LiAlH_4$, Et_2O, 0 °C → reflux; (d) propionyl chloride, Et_3N, CH_2Cl_2; (e) $HNO_3/H_2SO_4/H_2O$, $MeNO_2$, 0 °C; (f) separation of 6- and 8-nitrated product with column chromatography on SiO_2; (g) 10% Pd/C, H_2, EtOH; (h) $LiAlH_4$, Et_2O, 0 °C → reflux; (i) KSCN, Br_2, AcOH.

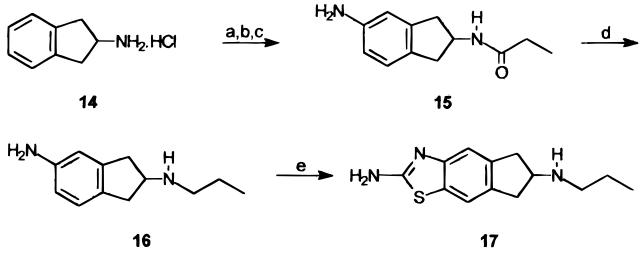
have free radical scavenging properties.[10] Pramipexole (**3**) was recently reported to have neuroprotective properties which are probably related to its antioxidant properties.[11]

These observations, together with the fact that 2-aminothiazoles are chemically easily accessible from anilines,[12] encouraged us to prepare a series of 3-amino-[1]benzopyran- or 2-aminoindan-derived 2-aminothiazoles and to investigate the concept of combining DA agonism with free radical scavenging properties in a single molecule.[5] This study describes the synthesis of five 3-amino-1-benzopyran- or 2-aminoindan-derived 2-aminothiazoles (compounds **12**, **13**, **17**, **20**, and **21**) and the pharmacological evaluation of their action on DA receptors. In addition, these compounds were tested for their ability to inhibit nonenzymatic lipid peroxidation.

Chemistry

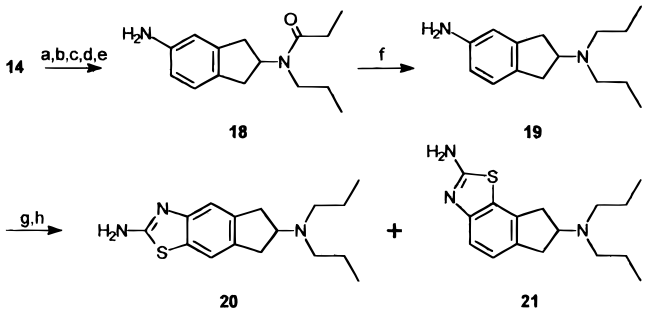
The synthesis of **12** and **13** is outlined in Scheme 1, starting from amino ketone **4**, which was prepared as described previously.[13] According to standard methods, amino ketone **4** was propionylated and the benzylic ketone was reduced catalytically (Pd/C). Then the amide was reduced with $LiAlH_4$, and a second propyl group was introduced by propionylation affording amide **5**.

Scheme 2[a]



[a] Reagents: (a) propionyl chloride, $NaHCO_3$, H_2O, EtOAc; (b) $HNO_3/H_2SO_4/H_2O$, $MeNO_2$, 0 °C; (c) NH_4CO_2H, 10% Pd/C, MeOH, 50 °C; (d) BH_3 in THF, Et_2O, rt → reflux; (e) KSCN, Br_2, AcOH.

Scheme 3[a]



[a] Reagents: (a) propionyl chloride, $NaHCO_3$, H_2O, EtOAc; (b) BH_3 in THF, Et_2O, rt → reflux; (c) propionyl chloride, Et_3N, CH_2Cl_2; (d) $HNO_3/H_2SO_4/H_2O$, $MeNO_2$, 0 °C; (e) NH_4CO_2H, 10% Pd/C, MeOH, 50 °C; (f) BH_3 in THF, Et_2O, rt → reflux; (g) KSCN, Br_2, AcOH; (h) separation of isomers with column chromatography on SiO_2.

Nitration of **5** was performed with a mild nitrating mixture to avoid double nitration,[14] and the 6- and 8-nitrated products (**6** and **7**, respectively) were separated with column chromatography on SiO_2. **6** and **7** were reduced catalytically to yield aniline amides **8** and **9**, respectively, which were reduced with $LiAlH_4$ to afford the aniline amines **10** and **11**, respectively. Finally, **10** and **11** were treated with potassium thiocyanate and bromine,[12] to give thiazolobenzopyrans **12** and **13**, respectively.

Compounds **17**, **20**, and **21** were synthesized analogously to the above-described synthesis of **12** and **13**, although some different reagents were used (Schemes 2 and 3).

Compound **17** was synthesized starting from 2-aminoindan **14** (Scheme 2) which was propionylated to give the intermediate amide, then nitrated[14] to give mainly the 5-nitrated product, and reduced to the aniline amide **15** with Pd/C and ammonium formate as hydrogen donor. Compound **15** was purified from the minor byproduct (probably 4-substituted product) with MPLC on SiO_2. Reduction of the amide was performed with BH_3 in THF,[9] to give aniline amine **16**. Reaction of **16** with potassium thiocyanate and bromine[12] afforded the aminothiazoloindan **17**, which was the only product of thiazole ring closure that was isolated.

Compounds **20** and **21** were synthesized analogously to **17**, but with the insertion of an extra reduction and propionylation step to obtain di-*n*-propyl products (Scheme 3). Briefly, 2-aminoindan **14** was propionylated and reduced to give the previously described 2-*N*-*n*-propylaminoindan.[15] Propionylation, subsequent nitration, and catalalytic reduction afforded the aniline

Table 1. Affinity for Human DA D_{2L}, D_3, and D_4 Receptors (left) and Inhibitory Properties on Lipid Peroxidation (LPO, right) of Thiazolobenzopyrans and Thiazoloindans (pramipexole (**3**, PPX) as reference compound)

	affinity for DA receptors, K_i[a] (nM)				inhib of LPO,
compd	D_{2L} (agonist radioligand)	D_{2L} [^{3}H]spip	D_3 [^{3}H]spip	$D_{4.2}$ [^{3}H]spip	IC_{50}[a] (μM)
12	47 ([^{3}H]N-0437)	5920	510	ND[b]	50
13	536 ([^{3}H]N-0437)	3510	1400	ND	5
17	1350 ([^{3}H]NPA)	ND	>10 μM	>3.33 μM	>100
20	27 ([^{3}H]NPA)	ND	1.4	272	60
21	500 ([^{3}H]NPA)	ND	11	IC_{50} > 10 μM	30
3[c]	ND	139[d]	2.78[d]	138[d]	neuroprotective[f]
(PPX)		2.07[e]	0.49[e]	2.76[e]	

[a] K_i and IC_{50} values are means of three separate experiments, the results of which did not vary by more than 25%. [b] ND means not determined. [c] Binding data from ref 8. [d] K_{iL}, low-affinity binding. [e] K_{iH}, high-affinity binding. [f] Pramipexole displays neuroprotective effects against postischemic or methamphetamine-induced degeneration of nigrostriatal neurons.[11]

amide **18**. Amide reduction gave aniline amine **19**, which was reacted with potassium thiocyanate and bromine,[12] to afford the products **20** and **21**, which could be separated with MPLC on SiO_2. NMR spectroscopy showed that these compounds were products of thiazole ring closure in two different directions.

Pharmacology

DA Receptor Binding. Aminothiazoles **12**, **13**, **17**, **20**, and **21** were tested for their in vitro binding affinity for human dopamine (DA) D_{2L}, D_3, or $D_{4.2}$ receptors, expressed in Chinese hamster ovary (CHO) K-1 cells. In the antagonist binding studies, the affinity of the compounds was determined by their ability to displace [^{3}H]spiperone from D_{2L}, D_3, or $D_{4.2}$ DA receptors. In the agonist binding studies, the affinity for the D_{2L} DA receptor was determined using [^{3}H]N-0437 (5-hydroxy-2-(*N*-*n*-propyl-*N*-(2-thienylethyl)amino)tetralin) or [^{3}H]-NPA (*N*-propylnorapomorphine) as the radioligand. The affinity data obtained with [^{3}H]NPA are comparable to those obtained with [^{3}H]N-0437. Receptor affinities are presented in Table 1.

Radical Scavenging Properties. The radical scavenging/antioxidant properties of the thiazoloindans and thiazolobenzopyrans were determined with the (non-enzymatic) lipid peroxidation assay.[16] In this assay, radical formation is iron-dependent and the peroxidation of polyunsaturated fatty acids within the microsomes is induced by the addition of 10 μM Fe^{2+}. By scavenging radicals the target compounds can inhibit lipid peroxidation. IC_{50} values are presented in Table 1.

Intrinsic Activity. The intrinsic activity (IA) of compounds **12**, **20**, and **21** was determined with a functional test, the mitogenesis assay.[17,18] [^{3}H]Thymidine uptake was determined in CHO-L6 cells transfected with the rat DA D_{2L} or D_3 receptor, as a measure of agonism at these receptors (Table 2). The IA was compared with that of quinpirole, which is a full agonist at both receptors (IA = 100%). In the same cells the ability of **12**, **20**, and **21** to inhibit quinpirole-stimulated [^{3}H]thymidine uptake was determined, which is a measure of antagonism (Table 2).

Contralateral Turning in 6-OH-DA Lesioned Rats. Compound **20** was further evaluated in rats unilaterally lesioned with 6-OH-DA (Figure 1). In this model, the DA neurons of one side (left or right) of the nigrostriatal DA system are selectively and completely degenerated by intracebral injection of the neurotoxin 6-OH-DA. This causes a postsynaptic supersensitivity to develop on the lesioned side.[19] Upon systemic administration of a DA agonist, the rat will start to turn contralaterally, i.e., toward the nonlesioned side.[20] The evoked turning behavior is a measure of the DA (D_1 and/or D_2) agonist properties of a compound.

Table 2. Agonist and Antagonist Effects of Selected Compounds as Measured in the Mitogenesis Assay at the Rat D_{2L} and D_3 Receptors

	[^{3}H]thymidine uptake EC_{50}, nM (IA[a])		inhib of quinpirole (30 nM)-stimulated [^{3}H]thymidine uptake	
compd	DA D_{2L}	DA D_3	DA D_{2L}	DA D_3
12	148 ± 23 (7% ± 1)	>1000 (0%)	A[b]	A
20	5.7 ± 2.2 (28% ± 7)	>1000 (0%)	A	A
21	18.7 ± 2.9 (71% ± 6)	>1000 (0%)	NA[c]	A
3 (PPX)[d]	1.7 ± 0.4 (90 ± 10%)	0.21 ± 0.04 (98 ± 2.2%)	NT[e]	NT
quinpirole	2.2 (100%)	1.7 (100%)	NA	NA

[a] IA means intrinsic activity. [b] A means active (test concentrations ranging from 0.1 nM to 1 μM). [c] NA means not active. [d] IA data from ref 8. [e] NT means not tested. All values are the means of three determinations ± SEM. Pramipexole (**3**, PPX) and quinpirole are included as reference compounds.

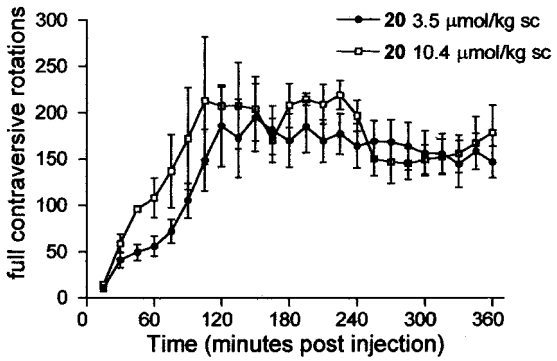


Figure 1. Effect on turning behavior of **20** in unilaterally 6-OH-DA lesioned rats. Each point is the mean ± SEM of five (3.5 μmol/kg) or three (10.4 μmol/kg) rats. Total number of full contraversive rotations for 3.5 μmol/kg: 3350 ± 460, for 10.4 μmol/kg: 3890 ± 390.

In addition, the effect of **20** was studied in combination with haloperidol (Figure 2), which selectively blocks DA D_2-like receptors. Rotation behavior was compared with an equal dose of **20**, combined with an ip injection of vehicle.

Furthermore, the rotation model was employed to study the oral availability of compound **20**. Figure 3 depicts the rotation behavior of orally (po) administered

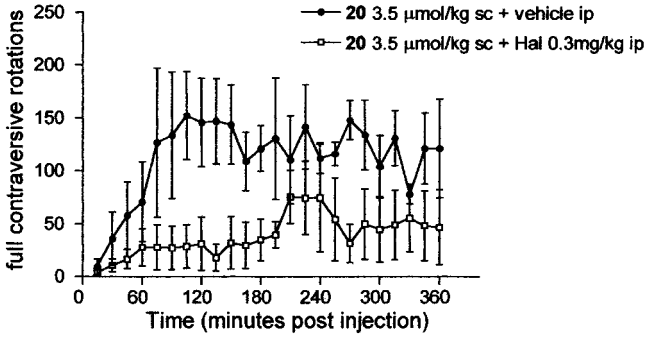


Figure 2. Effect on turning behavior of **20** alone or in combination with haloperidol, in unilaterally 6-OH-DA lesioned rats. Each point is the mean ± SEM of four rats. Total number of full contraversive rotations for 3.5 μmol/kg + vehicle: 2700 ± 670, for 3.5 μmol/kg + haloperidol: 930 ± 510.

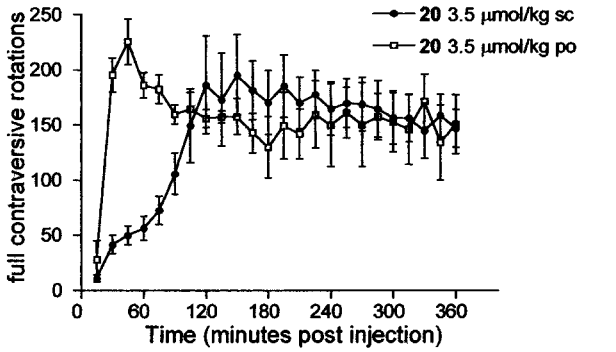


Figure 3. Effect on turning behavior of **20** administered orally (po) or subcutaneously (sc). Each point is the mean ± SEM of four (po) or five (sc) rats. Total number of full contraversive rotations for 3.5 μmol/kg sc: 3350 ± 460, for 3.5 μmol/kg po: 3700 ± 390.

20 in comparison with an equal dose administered subcutaneously (sc).

Microdialysis in Rat Striatum. The effects of **20** on in vivo DA turnover in rat striatum were assessed with microdialysis methods (Figure 4).

Results and Discussion

DA Receptor Binding. Both 3-amino-1-benzopyrans[21] and 2-aminoindans,[22] substituted with a hydroxy group on the aromatic ring, are known templates for DA agonists. In these molecules, both the phenolic oxygen and the basic amine are supposed to interact with the receptor binding sites. Strictly speaking, the 2-aminothiazole moiety, as used in the here-described aminothiazoles, is not a bioisosteric replacement of the phenol group but rather an extension of the aromatic part of the molecule. Nevertheless, the aminothiazole exocyclic amino group may substitute for the hydroxy group of a phenol or catechol and form a hydrogen bond with the receptor. The position of this amino group relative to the aromatic nucleus and basic nitrogen probably plays a critical role for DA receptor affinity. This may explain the low affinity of the thiazolobenzopyrans **12** and **13** for DA receptors (Table 1).

The thiazoloindans show a more interesting DA receptor binding profile. Compared to the thiazolobenzopyrans, di-*n*-propylthiazoloindans **20** and **21** show a higher affinity for DA D_3 receptors.

The affinity of the thiazoloindans is remarkably increased when a second *n*-propyl group is introduced

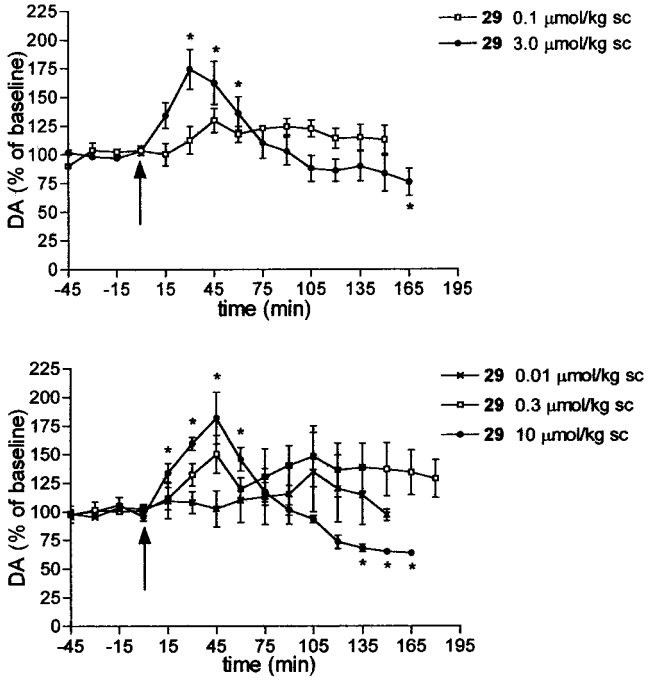


Figure 4. Effect of **20** on DA turnover in rat striatum. Each point is the mean ± SEM of three to four determinations. The arrow indicates the time of injection. *$p < 0.05$ vs time = 0 min.

in the 2-aminoindan structure. Especially the affinity for the DA D_3 receptor of di-*n*-propyl compound **20** is enormously increased, as compared to that of the monopropyl analogue **17**. Such an effect is not observed in the related 2-aminotetralin series, where introduction of a second *n*-propyl group only marginally increases affinity for the DA D_3 receptor and even decreases affinity for the DA D_{2L} receptor subtype (if measured with an agonist radioligand).[23]

Unexpectedly, compounds **20** and **21** display an interesting DA D_3-preferring binding profile. Compound **20** binds with moderate affinity to DA D_2 and with high affinity to DA D_3 receptors (see Table 1). Although **20** is "quasi-symmetrical" (its asymmetry is created by the inequivalency of the thiazole nitrogen and sulfur atoms), resolving this compound may reveal even higher DA D_3 selectivity for one of its enantiomers.

The DA receptor binding profile of **12**, **20**, and **21** encouraged us to study the action of these compounds on DA D_2 and D_3 receptors in a functional assay (see below).

Radical Scavenging Properties. As shown in Table 1, the thiazolobenzopyrans and thiazoloindans inhibit lipid peroxidation, although with marked potency differences. This inhibition may be caused by radical scavenging properties of the test compounds. However, within this assay other processes (like iron chelation) may play a role in the observed inhibition. Insofar as these processes actually take place within lipid membranes, the observed lower potency of the monopropyl analogue **17** may be explained by its lower lipophilicity (log $D = 0.19$ for **17**, compared to log $D = 1.66$ for **20**, as predicted with the computer program Pallas 1.2[24]).

In contrast to DA agonism or antagonism, the process of free radical scavenging is not a specific interaction with a protein. The scavenger has to compete with

various cell components for reactive species. As a consequence, a radical scavenging drug probably needs to be dosed in high amounts to exert an effect in vivo. For the above-described compounds it remains to be established whether radical scavenging properties in vitro will provide neuroprotective properties in vivo.

Intrinsic Activity. The action of compounds **12**, **20**, and **21** at DA D_{2L} and D_3 receptors was assessed in the mitogenesis assay: agonism stimulates cell division, which can be measured with uptake of [^{3}H]thymidine.

From the results listed in Table 2 it can be concluded that compounds **20** and **21** display (partial) agonism at DA D_2 sites and antagonism at DA D_3 sites, whereas **12** appears to be an antagonist at both receptors (but with low potency). This contrasts with the related 2-aminothiazole pramipexole (**3**), which is a full agonist at both DA D_2 and D_3 receptors.[8] The observed potencies (EC_{50} values) to stimulate [^{3}H]thymidine uptake reflect in part the DA D_2 affinity: compound **20** (K_i D_2 = 27 nM) displays the highest potency at DA D_2 receptors, whereas the potency of compound **21** is higher than expected, regarding its receptor binding profile.

Taking the intrinsic activity data and receptor binding profile together, it can be concluded that compound **20** is a potent and partially selective antagonist at DA D_3 receptors. In addition, it displays partial agonism at DA D_2 receptors, but with a moderate affinity and potency.

Contralateral Turning in 6-OH-DA Lesioned Rats and Microdialysis in Rat Striatum. The DA agonist properties of **20** were evaluated in rats with a unilaterally lesioned nigrostriatal DA system. Also, the effects of (several doses of) **20** on DA turnover in rat striatum were studied.

As is obvious from Figure 1, compound **20** produced a strong and long-lasting activation of rotation behavior. Furthermore, **20** caused a dose-dependent increase of DA turnover in rat striatum (Figure 4). On first sight, these observations seem contradictory: An activation of rotation behavior in unilaterally 6-OH-DA lesioned rats implies agonism at postsynaptic receptors, whereas an increase of DA turnover (due to the blockade of presynaptic DA receptors) as measured with microdialysis would imply antagonism.

Carlsson proposed that the extent of previous (endogenous) agonist occupancy determines DA receptor responsiveness and thereby in part the intrinsic efficacy of agents interacting with the receptors.[25] This proposition was based on the pharmacology of the partial agonist (−)-3-(3-hydroxyphenyl)-*N*-*n*-propylpiperidine ((−)-3-PPP), which was found to act as an agonist in pharmacological models with supersensitive DA receptors and as an antagonist on normosensitive DA receptors.[26] The dual character of compound **20** also appears to be accounted for by its partial agonism at DA D_2 receptors. In unilaterally 6-OH-DA lesioned rats, a postsynaptic supersensitivity of DA receptors in striatum develops,[19] which "amplifies" the DA agonist action of a compound. In this situation, the DA agonist properties of compound **20** predominate, which explains the observed rotation activation. On the other hand, in nonpretreated rats used in the microdialysis experiments, DA receptors are normosensitive. In this situation, the antagonist properties of compound **20** predominate, and a blockade of presynaptic DA receptors would then explain the observed increase in DA turnover.

Compound **20** was also tested in rats which were reserpinized 18 h beforehand (data not shown), where it turned out to be inactive. In reserpinized rats postsynaptic DA receptors are relatively insensitive, and the partial DA D_2 agonism of **20** does not give an effect in this model.

The potent DA D_3 antagonism of **20** may contribute to the observed profile. As has been suggested previously, the DA D_3 receptor may be either a postsynaptic receptor with an inhibitory influence on rat locomotor activity[27,28] or a striatal autoreceptor with a DA synthesis inhibiting influence,[29] or both. As a consequence, blockade of postsynaptic DA D_3 receptors by **20** may produce increased locomotor activity. In microdialysis, blockade of DA D_3 autoreceptors may increase DA synthesis. However, in rats the striatal density of DA D_3 receptors is believed to be relatively low. Further pharmacological evaluation of compound **20** may reveal the actual role of DA D_3 receptors in the observed profile.

Within this model, activation of rotation may reflect activation of DA D_1 or D_2 receptors, or a combined activation of both DA D_1 and D_2 receptors. Administration of haloperidol blocks the activation of DA D_2(-like) receptors. Figure 2 displays the effects of **20** in combination with haloperidol. It was observed that haloperidol greatly reduces the rotation activation of **20**, thereby excluding activation of DA D_1 receptors by this compound.

The oral activity of **20** was also studied with unilaterally 6-OH-DA lesioned rats. As can be seen in Figure 3, compound **20** has an excellent oral activity, which is comparable to its activity upon subcutaneous administration. To our surprise, orally administered **20** gives a faster onset of action as compared to subcutaneous administration. This may be explained by a slow subcutaneous diffusion process after administration of **20** in the neck region. Alternatively, the quicker onset of action after oral administration of **20** might be explained by the formation of active metabolites.

In the microdialysis experiments we observed that, after an initial increase in DA turnover, compound **20** causes a (dose-dependent) decrease of DA turnover (Figure 4: 3 and 10 μmol/kg). This may be explained with different receptor binding and agonist/antagonist properties of the two enantiomers of **20**. One of the enantiomers may have more intrinsic (agonist) activity than the other, and this effect may predominate in the course of the experiments, which causes the observed decrease of DA turnover. If this is true, the situation compares to the observed differences for the enantiomers of 3-PPP: (+)-3-PPP was found to behave as a full agonist, whereas (−)-3-PPP displayed agonist and antagonist actions, which depended on the DA receptor which was studied (pre- or postsynaptic)[26] and the state it was in (super- or normosensitive).[30]

In view of this (one of the enantiomers of) compound **20** may deserve closer examination as a potential (atypical) antipsychotic. Selective stimulation of dopaminergic autoreceptors decreases DA synthesis via negative feedback, thereby decreasing dopaminergic neurotransmission. As has been suggested for (−)-3-

PPP[26] and other DA autoreceptor-selective agents, this approach may lead to antipsychotic action without the concomitant side effects observed for the classical neuroleptics.

In conclusion, compound **20** is a partial DA D_2 agonist, with excellent oral activity. The long-lasting activity and excellent oral activity in unilaterally 6-OH-DA lesioned rats suggest that compound **20** is potentially useful for the treatment of PD. In addition, **20** displays selective DA D_3 antagonism. Whether this contributes to the observed in vivo actions of **20** remains to be studied. Furthermore, the potential neuroprotective properties of compound **20** and its analogues may prove valuable in the treatment of PD.

Resolution of **20** is needed for further pharmacological investigations. This may reveal different DA agonist or antagonist actions for the enantiomers of **20** and possibly a difference in the preference for DA autoreceptors. The potential antipsychotic action of (one of the enantiomers of) **20** needs further study.

Experimental Section

Chemistry. General. Melting points were determined in open glass capillaries on an Electrothermal digital melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 200 MHz on a Varian Gemini 200 spectrometer; the chemical shifts are given in δ units (ppm) relative to the solvent. Coupling constants are given in hertz (Hz). The spectra recorded were consistent with the proposed structures of intermediates and final compounds. IR spectra were obtained on an ATI-Mattson spectrophotometer, and only the important absorptions are given. Electronic ionization (EI) mass spectra were obtained on a Unicam 610-Automass 150 GC−MS system. Elemental analyses were performed by the Analytical Chemistry Section at Parke Davis, Ann Arbor, MI, and were within 0.4% of the theoretical values, except where noted. Compounds that were obtained as an oil, or as a solid in a very small amount, were analyzed by high-resolution mass spectrometry (HRMS), performed on a JEOL MSroute JMS-600H by the Department of Chemistry, University of Groningen.

If necessary, compounds were purified with medium-pressure chromatography (MPLC) on silica gel, starting with an apolar eluent (usually 100% hexane) and gradually increasing its polarity (usually by adding ethyl acetate), finishing with an eluent mixture that gave a R_f value of approximately 0.3 on TLC.

Materials. The starting compounds 3,4-dihydro-2*H*-[1]-benzopyran-4-one (4-chromanone) and 2-aminoindan hydrochloride were purchased from Acros and Aldrich, respectively. All other reagents and solvents were also commercially available and were used without further purification, with the exception of diethyl ether, which was distilled from sodium/benzophenone.

3-(*N*-*n*-Propyl-*N*-propionylamino)-3,4-dihydro-2*H*-[1]-benzopyran (5). 3-*N*-*n*-Propylamino-3,4-dihydro-2*H*-[1]benzopyran (2.95 g, 15.5 mmol) was dissolved in 50 mL of methylene chloride, and triethylamine (4.3 mL, 30 mmol) was added. A solution of propionyl chloride (1.6 mL, 18.5 mmol) in 15 mL of methylene chloride was added dropwise over a 30-min period. After the addition was completed, the reaction mixture was stirred for 30 min. The mixture was washed with water, then with brine and dried over $MgSO_4$. Evaporation of the solvent gave a brown oil, which was purified with column chromatography (eluent diethyl ether:hexane = 2:1), yielding **5** as a yellow oil (2.72 g, 71%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.87 (t, J = 7.2, 3H), 1.10−1.19 (m, 5H), 1.49−1.65 (m, 2H), 2.36 (q, J = 7.3, 2H), 2.89 (dd, J_1 = 15.7, J_2 = 5.7, 1H), 3.12−3.31 (m, 2H), 4.14−4.44 (m, 2H), 6.80−7.14 (m, 4H); ^{13}C NMR δ 9.3, 11.0, 23.8, 26.7, 28.5, 48.0, 49.9, 67.3, 116.5, 120.6, 127.3, 129.7, 138.5, 155.6, 174.2; HRMS calcd (obsd) for $C_{15}H_{21}NO_2$ 247.1572 (247.1580).

6- and 8-Nitro-3-(*N*-*n*-propyl-*N*-propionylamino)-3,4-dihydro-2*H*-[1]benzopyran (6 and 7). Amide **5** (1.7 g, 6.9 mmol) was dissolved in nitromethane (22 mL), and cooled on ice. A nitrating mixture consisting of 0.51 mL concentrated nitric acid, 1.17 mL of water and 6.92 mL of concentrated sulfuric acid was added dropwise over a 20-min period. After the addition was completed the reaction mixture was stirred on ice for 45 min. The reaction was quenched with ice, and the reaction mixture was extracted with ethyl acetate. The combined organic layers were washed once with brine, dried over $MgSO_4$, and concentrated under reduced pressure, which gave a brown oil. The two products were separated with column chromatography (eluent 100% Et_2O), which yielded 1.12 g of the 6-nitrated product as a brown oil (55%, R_f = 0.35 in 100% Et_2O) and 0.63 g of the 8-nitrated product as a brown oil (31%, R_f = 0.26 in 100% Et_2O). Both nitro products solidified upon standing and were used without further purification.

6-Nitro-3-(*N*-*n*-propyl-*N*-propionylamino)-3,4-dihydro-2*H*-[1]benzopyran (6): mp 109−111 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.89 (t, J = 7.4, 3H), 1.12 (t, J = 7.4, 3H), 1.49−1.64 (m, 2H), 2.35 (q, J = 7.4, 2H), 2.85−2.94 (m, 1H), 3.13−3.21 (m, 2H), 3.36−3.46 (m, 1H), 4.22−4.35 (m, 2H), 4.40−4.50 (m, 1H), 6.85 (d, J = 9.6, 1H), 7.93−7.96 (m, 2H); ^{13}C NMR δ 9.4, 11.1, 23.9, 27.0, 28.5, 48.8, 50.1, 67.8, 117.1, 121.7, 123.6, 126.0, 141.2, 159.5, 174.3; MS (EIPI) *m/e* 292 (M^+). Anal. ($C_{15}H_{20}N_2O_4 \cdot {}^1/_4H_2O$) C,H,N.

8-Nitro-3-(*N*-*n*-propyl-*N*-propionylamino)-3,4-dihydro-2*H*-[1]benzopyran (7): mp 93−95 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.89 (t, J = 7.4, 3H), 1.12 (t, J = 7.4, 3H), 1.49−1.64 (m, 2H), 2.35 (q, J = 7.4, 2H), 2.88−2.99 (m, 1H), 3.16−3.24 (m, 2H), 3.42−3.57 (m, 1H), 4.11−4.36 (m, 2H), 4.49−4.59 (m, 1H), 6.88−6.97 (m, 1H), 7.26 (d, J = 6.3, 1H), 7.67 (d, J = 7.7, 1H); ^{13}C NMR δ 9.4, 11.2, 23.7, 27.1, 28.7, 49.4, 50.6, 68.0, 120.0, 123.7, 124.6, 134.5, 139.4, 158.8, 174.2; MS (EIPI) *m/e* 292 (M^+). Anal. ($C_{15}H_{20}N_2O_4$) C,H,N.

6-Amino-3-(*N*-*n*-propyl-*N*-propionylamino)-3,4-dihydro-2*H*-[1]benzopyran (8). A solution of **6** (0.80 g, 2.7 mmol) in 100 mL of ethanol was treated (under N_2) with 10% Pd/C (0.8 g), placed in a Parr apparatus, and shaken for 2 h with a hydrogen gas pressure of 4.5 atm. The Pd/C was removed by filtration over Celite, and the solvent was removed under reduced pressure, which yielded **8** as a light-red oil (0.61 g, 85%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.84 (t, J = 7.4, 3H), 1.13 (t, J = 7.3, 3H), 1.49−1.61 (m, 2H), 2.28−2.40 (m, 2H), 2.73−2.84 (m, 1H), 3.04−3.16 (m, 3H), 3.59 (br s, 2H), 4.04−4.24 (m, 2H), 4.41−4.46 (m, 1H), 6.38 (s, 1H), 6.45 (d, J = 8.4, 1H), 6.62 (d, J = 8.4, 1H); ^{13}C NMR δ 9.3, 11.0, 23.8, 26.6, 28.5, 47.9, 49.9, 67.3, 115.1, 115.9, 117.0, 121.4, 139.7, 147.0, 174.2; HRMS calcd (obsd) for $C_{15}H_{22}N_2O_2$ 262.1681 (262.1696).

8-Amino-3-(*N*-*n*-propyl-*N*-propionylamino)-3,4-dihydro-2*H*-[1]benzopyran (9). Compound **7** (0.63 g, 2.2 mmol) was converted to **9** (0.47 g, 83%), as described for **6**, and was obtained as a light-brown oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.87 (t, J = 7.3, 3H), 1.15 (t, J = 7.3, 3H), 1.52−1.64 (m, 2H), 2.30−2.43 (m, 2H), 2.78−2.90 (m, 1H), 3.11−3.19 (m, 3H), 3.70 (br s, 2H), 4.16−4.34 (m, 2H), 4.40−4.55 (m, 1H), 6.44−6.73 (m, 3H); ^{13}C NMR δ 9.3, 11.0, 23.9, 26.7, 28.3, 47.9, 50.0, 67.4, 112.8, 118.9, 120.5, 120.7, 135.3, 141.8, 174.2; HRMS calcd (obsd) for $C_{15}H_{22}N_2O_2$ 262.1681 (262.1709).

6-Amino-3-(*N*,*N*-di-*n*-propylamino)-3,4-dihydro-2*H*-[1]-benzopyran (10). $LiAlH_4$ (0.23 g, 5.7 mmol) was suspended in 4.5 mL of dry ether, and the suspension was cooled on ice. A solution of amide **8** (0.60 g, 2.3 mmol) in 75 mL of dry ether was added dropwise. After the addition was completed, the mixture was stirred on ice for 1 h, then at room temperature for 1 h, and then heated to reflux for 2h. After cooling to room temperature, the reaction was quenched by the cautious addition of 0.23 mL of water, 0.23 mL of 4 N NaOH and 0.69 mL of water (in that order). The mixture was heated to reflux until all precipitates had turned white (10 min), cooled to room

temperature, and filtered over Celite. The filtrate was dried over Na_2SO_4 and concentrated under reduced pressure, which yielded **10** as a brown oil (0.51 g, 89%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.87 (t, J = 7.3, 6H), 1.36−1.50 (m, 4H), 2.46−2.53 (m, 4H), 2.75 (d, J = 8.6, 2H), 3.08−3.22 (m, 3H), 3.74 (t, J = 10.3, 1H), 4.22 (dd, J_1 = 10.3, J_2 = 7.3, 1H), 6.42−6.49 (m, 2H), 6.63 (d, J = 8.8, 1H); ^{13}C NMR δ 11.5 (2C), 21.6 (2C), 28.2, 52.5 (2C), 53.3, 67.8, 114.8, 116.3, 116.7, 122.4, 139.5; HRMS calcd (obsd) for $C_{15}H_{24}N_2O$ 248.1889 (248.1891).

8-Amino-3-(*N*,*N*-di-*n*-propylamino)-3,4-dihydro-2*H*-[1]-benzopyran (11). Compound **9** (0.46 g, 1.8 mmol) was converted to **11** (0.41 g, 92%), as described for **8**, and was obtained as an oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.88 (t, J = 7.3, 6H), 1.37−1.55 (m, 4H), 2.47−2.55 (m, 4H), 2.81 (d, J = 8.3, 2H), 3.08−3.28 (m, 1H), 3.65 (br s, 2H), 3.81 (t, J = 10.3, 1H), 4.36 (dd, J_1 = 10.3, J_2 = 3.1, 1H), 6.45−6.72 (m, 3H); ^{13}C NMR δ 11.5 (2C), 21.5 (2C), 27.8, 52.5 (2C), 53.3, 68.0, 112.7, 119.4, 120.4, 121.5, 135.2, 142.2; HRMS calcd (obsd) for $C_{15}H_{24}N_2O$ 248.1889 (248.1895).

6-Amino-3-(*N*,*N*-di-*n*-propylamino)-3,4-dihydro-2*H*-thiazolo[5,4-*f*]-[1]benzopyran (12). Aniline **10** (0.20 g, 0.80 mmol) and potassium thiocyanate (0.16 g, 1.66 mmol) were dissolved in 1.9 mL of glacial acetic acid. A solution of bromine (40 μL, 0.80 mmol) in 0.9 mL of glacial acetic acid was added dropwise over a period of 15 min. After the addition was completed, the reaction mixture was stirred for 1.5 h, then basified with 10% NaOH and extracted with ethyl acetate. The combined organic layers were washed once with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The product was purified with column chromatography over silica (eluent 100% Et_2O) which yielded **12** as a white solid (0.11 g, 45%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.90 (t, J = 7.4, 6H, $-CH_3$), 1.39−1.57 (m, 4H, $-CH_2$-), 2.50−2.57 (m, 4H, $-N-CH_2$-), 2.72−2.89 (m, 2H, Ph-CH_2-), 3.23−3.33 (m, 1H, −CH−N-), 3.84 (t, J = 10.3, 1H, −O−CH-), 4.29−4.35 (m, 1H, −O−CH-), 5.62 (s, 2H, $-NH_2$), 6.81 (d, J = 8.6, 1H, PhH), 7.27 (d, J = 8.6, 1H, PhH); ^{13}C NMR δ 11.7 (2C), 22.0 (2C), 28.1, 52.7 (2C), 53.2, 68.0, 114.8, 115.0, 117.6, 132.4, 145.5, 150.0, 164.0; IR (KBr, cm^{-1}) 2968, 2632, 1645, 1580, 1484; MS (EIPI) *m*/*e* 305 (M^+). The product was converted to the dihydrochloride and recrystallized from ethanol, yielding an off-white solid: mp 209−212 °C. Anal. ($C_{16}H_{23}N_3SO\cdot 2HCl\cdot H_2O$) C,H,N.

8-Amino-3-(*N*,*N*-di-*n*-propylamino)-3,4-dihydro-2*H*-thiazolo[5,4-*h*]-[1]benzopyran (13). Aniline **11** (0.14 g, 0.57 mmol) was converted to **13** (0.095 g, 55%), as described for **10**, and was obtained as a light-brown oil. The product failed to crystallize as the dihydrochloride: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.91 (t, J = 7.3, 6H, $-CH_3$), 1.40−1.58 (m, 4H, $-CH_2-$), 2.44−2.80 (m, 4H, $-N-CH_2-$), 2.85−2.95 (m, 1H, Ph−CH−), 3.03−3.07 (m, 1H, Ph−CH−), 3.14−3.26 (m, 1H, −CH−N−), 3.84 (t, J = 10.2, 1H, −O−CH−), 4.05 (s, 2H, $-NH_2$), 4.34−4.42 (m, 1H, −O−CH−), 6.55 (d, J = 8.3, 1H, PhH), 7.08 (d, J = 8.3, 1H, PhH); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 11.5 (2C), 21.8 (2C), 26.7, 52.6 (2C), 53.1, 67.8, 108.8, 110.6, 111.6, 112.5, 128.1, 138.6, 166.5; IR (KBr, cm^{-1}) 2966, 2353, 1632, 1485; HRMS calcd (obsd) for $C_{16}H_{23}N_3OS$ 305.1562 (305.1547).

5-Amino-2-propionamidoindan (15). 2-Propionamidoindan (1.0 g, 5.5 mmol) was dissolved in nitromethane (18 mL), and cooled on ice. A nitrating mixture consisting of 0.74 mL concentrated nitric acid, 1.6 mL of water and 10 mL of concentrated sulfuric acid was added dropwise over a 30-min period. After the addition was completed, the reaction mixture was stirred for 1 h, while gradually warming to room temperature. The reaction was quenched with ice, and the reaction mixture was extracted with ethyl acetate. The combined organic layers were washed once with brine, dried over $MgSO_4$, and concentrated under reduced pressure, yielding a yellow solid (1.2 g, 95%), which consisted mainly (82% according to GC) of 5-nitro-2-propionamidoindan.

The nitro compound (1.2 g, containing 4.3 mmol of 5-nitro-2-propionamidoindan) and ammonium formate (1.4 g, 22.2 mmol) were dissolved in 55 mL of methanol. This mixture was treated (under N_2) with 10% Pd/C (0.56 g) and subsequently stirred at 50 °C for 45 min. After cooling to room temperature, the Pd/C was removed by filtration over Celite, and the methanol was evaporated under reduced pressure. The remaining pink solid was purified with MPLC on silica (initial eluent 100% hexane, final eluent 100% ethyl acetate). The pure fractions were pooled and concentrated to dryness, which gave **15** as a white solid (0.67 g, 76%): mp 127−128 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.08 (t, J = 7.7, 3H), 2.10 (q, J = 7.6, 2H), 2.62 (dt, J_1 = 16.1, J_2 = 4.2, 2H), 3.14 (dd, J_1 = 16.2, J_2 = 7.1, 2H), 3.61 (s, 2H), 4.59−4.67 (m, 1H), 6.12 (d, J = 7.3, 1H), 6.45−6.51 (m, 2H), 6.94 (d, J = 7.8, 1H); ^{13}C NMR δ 9.6, 29.4, 38.9, 40.0, 50.5, 111.5, 113.7, 125.1, 130.5, 142.2, 145.4, 173.6; MS (EIPI) *m*/*e* 204 (M^+). Anal. ($C_{12}H_{16}N_2O$) C,H,N.

5-Amino-2-*N*-*n*-propylaminoindan (16). Amide **15** (0.62 g, 3.0 mmol) was dissolved in 8 mL of dry ether, and BH_3 (16 mL of a 1 M solution in THF) was added dropwise, over a 1-h period. After the addition was completed, the reaction mixture was heated to reflux for 1 h. The mixture was cooled to room temperature, and 1.6 mL of water was added cautiously. Subsequently, 3.2 mL of 10% HCl was added, and all volatile solvents were evaporated under reduced pressure. The remaining aqueous solution was basified with 10% NaOH and extracted with ethyl acetate (2 × 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure, which yielded **16** as a clear oil (0.52 g, 90%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.92 (t, J = 7.3, 3H), 1.43−1.61 (m, 2H), 2.58−2.71 (m, 4H), 3.00−3.11 (m, 2H), 3.52−3.65 (m, 4H), 6.49 (d, J = 7.8, 1H), 6.55 (s, 1H), 6.96 (d, J = 7.8, 1H); ^{13}C NMR δ 11.6, 23.2, 38.9, 39.9, 50.0, 59.8, 111.5, 113.4, 125.0, 131.6, 142.9, 145.0; MS (EIPI) *m*/*e* 190 (M^+). Part of the product was converted to the dihydrochloride and recrystallized from ethanol, yielding white crystals: mp 238−242 °C. Anal. ($C_{12}H_{18}N_2\cdot 2HCl$) C,H,N.

6-Amino-2-*N*-*n*-propylaminothiazolo[4,5-*f*]indan (17). Compound **16** (0.48 g, 2.5 mmol) was converted to **17** (0.29 g, 46%), as described for **10**. The product was converted to the dihydrochloride and recrystallized from methanol/ethanol, which yielded a white solid: mp 285−290 °C; ^{1}H NMR (D_2O, 200 MHz) δ 0.81 (t, J = 7.3, 3H, $-CH_3$), 1.48−1.60 (m, 2H, $-CH_2-$), 2.92 (t, J = 7.7, 2H, $-N-CH_2-$), 2.96−3.08 (m, 2H, $PhCH_2-$), 3.26−3.38 (m, 2H, $PhCH_2-$), 3.95−4.08 (m, 1H, −CH−N−), 7.15 (s, 1H, PhH), 7.40 (s, 1H, PhH); ^{13}C NMR δ 9.9, 19.1, 34.9, 35.2, 47.5, 57.9, 109.7, 118.3, 121.9, 136.1, 136.2, 139.5, 169.2; IR (KBr, cm^{-1}) 2967, 2805, 2658, 1651, 1459; MS (EIPI) *m*/*e* 247 (M^+). Anal. ($C_{13}H_{17}N_3S_1\cdot 2HCl\cdot {}^1/_2H_2O$) C,H,N.

5-Amino-2-(*N*-*n*-propyl-*N*-propionyl)aminoindan (18). 2-(*N*-*n*-Propyl-*N*-propionyl)aminoindan (0.70 g, 3.0 mmol) was converted to 5-nitro-2-(*N*-*n*-propyl-*N*-propionyl)aminoindan, which subsequently was reduced to **18** as described for the conversion of 2-propionamidoindan to **15**. The product was purified with MPLC on silica (initial eluent 100% hexane, final eluent hexane:ethyl acetate = 1:1), yielding **18** as a light-yellow oil (0.49 g, 66%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.83 (t, J = 7.3, 3H), 1.15 (t, J = 7.3, 3H), 1.48−1.65 (m, 2H), 2.32−2.43 (m, 2H), 2.93−3.01 (m, 4H), 3.05−3.21 (m, 2H), 3.61 (br s, 2H), 4.60−4.77 (m, $^1/_2$H), 5.10−5.28 (m, $^1/_2$H), 6.50 (d, J = 7.6, 1H), 6.54 (s, 1H), 6.96 (d, J = 7.6, 1H); ^{13}C NMR (CD_3OD, 200 MHz) δ 8.6, 10.0, 22.4, 26.3, 35.9, 36.0, 43.9, 57.1, 111.4, 114.3, 124.2, 130.4, 141.5, 145.4, 175.0; HRMS calcd (obsd) for $C_{15}H_{22}N_2O$ 246.1732 (246.1720).

5-Amino-2-(*N*,*N*-di-*n*-propylamino)indan (19). Compound **18** (0.43 g, 1.8 mmol) was converted to **19** (0.39 g, 96%) as described for **15** and was obtained as an oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.88 (t, J = 7.3, 6H), 1.42−1.57 (m, 4H), 2.47−2.55 (m, 4H), 2.77−3.00 (m, 4H), 3.55−3.67 (m, 1H), 6.49 (d, J = 7.8, 1H), 6.54 (s, 1H), 6.95 (d, J = 7.8, 1H); ^{13}C NMR δ 11.7 (2C), 19.7 (2C), 35.4, 36.5, 53.2 (2C), 63.3, 111.3, 113.4, 124.8, 131.8, 142.9, 144.9; HRMS calcd (obsd) for $C_{15}H_{24}N_2$ 232.1939 (232.1936).

6-Amino-2-(*N*,*N*-di-*n*-propylamino)thiazolo[4,5-*f*]indan (20) and 5-Amino-2-(*N*,*N*-di-*n*-propylamino)thiazolo[5,4-*e*]indan (21). Compound **19** (0.35 g, 1.5 mmol) was converted to a mixture of **20** and **21**, as described for **10**. The

products were separated with MPLC on silica (initial eluent hexane:ethyl acetate = 1:1, final eluent ethyl acetate:ethanol = 1:1), which yielded **20** as a light-yellow solid (0.18 g, 41%) and **21** as a light-yellow solid (0.11 g, 25%).

20: ^{1}H NMR (CD_3OD, 200 MHz) δ 0.94 (t, J = 7.3, 6H, $-CH_3$), 1.57−1.66 (m, 4H, $-CH_2-$), 2.70−2.78 (m, 4H, $-N-CH_2-$), 2.92−3.25 (m, 4H, $PhCH_2-$), 3.65−3.88 (m, 1H, $-CH-N-$), 7.20 (s, 1H, PhH), 7.37 (s, 1H, PhH); ^{13}C NMR δ 10.3 (2C), 17.8 (2C), 35.1, 35.4, 52.5 (2C), 63.3, 113.1, 116.0, 129.1, 134.0, 138.4, 150.8, 168.2; IR (KBr, cm^{-1}) 2967, 2632, 1638; MS (EIPI) *m/e* 289 (M^+). The compound was converted to the dihydrochloride and recrystallized from 100% ethanol, which yielded an off-white solid: mp 273−275 °C dec. Anal. ($C_{16}H_{23}N_3S\cdot 2HCl\cdot {}^1/_2H_2O$) C,H,N.

21: ^{1}H NMR (CD_3OD, 200 MHz) δ 0.89 (t, J = 7.3, 6H, $-CH_3$), 1.46−1.57 (m, 4H, $-CH_2-$), 2.49−2.57 (m, 4H, $-N-CH_2-$), 2.72−3.18 (m, 4H, $Ph-CH_2-$), 3.52−3.78 (m, 1H, $-CH-N-$), 7.06 (d, J = 8.1, 1H, PhH), 7.18 (d, J = 8.1, 1H, PhH); ^{13}C NMR δ 10.6 (2C), 18.7 (2C), 35.6, 35.8, 52.6 (2C), 62.9, 115.7, 121.4, 126.0, 133.4, 134.7, 150.8, 167.5; IR (KBr, cm^{-1}) 2966, 2717, 2633, 1637, 1458; MS (EIPI) *m/e* 289 (M^+). The compound was converted to the dihydrochloride and recrystallized from 100% ethanol, which yielded an off-white solid: mp 233−237 °C dec; HRMS calcd (obsd) for $C_{16}H_{23}N_3S$ 289.1613 (289.1619).

Pharmacology. General. All experimental drugs tested were in the dihydrochloride form and could easily be dissolved in saline.

Receptor Binding. All receptor binding studies were performed at Parke Davis Pharmaceutical Research Division, by T. A. Pugsley. Binding to cloned human DA D_2, D_3, and D_4 receptors was carried out as described previously.[23]

Radical Scavenging Properties. The radical scavenging properties were determined at the Department of Pharmacochemistry, Vrije Universiteit Amsterdam, by G. Haenen. Lipid peroxidation was measured in rat liver microsomes as previously decribed.[16] Lipid peroxidation was induced by Fe^{2+} and ascorbate (final concentrations 10 μM and 0.2 mM, respectively). Lipid peroxidation was assayed by measuring the amount of thiobarbituric acid reactive material. The difference in absorbance at 535 and 600 nm ($\Delta A_{535-600}$) was determined.

Intrinsic Activity. The intrinsic activity determinations were performed at Pharmacia Corp., CNS Diseases Research, by M. E. Lajiness, as described in refs 17, 18.

Contralateral Turning in 6-OH-DA Lesioned Rats. Contralateral turning experiments were performed at Parke Davis Pharmaceutical Research Division, by L. Meltzer, as described in ref 31. Rats were food-deprived overnight for the po experiments with compound **20**.

Microdialysis in Rat Striatum. Microdialysis experiments were performed at the Department of Medicinal Chemistry, University of Groningen, by N. Rodenhuis, as described in ref 31. Statistics: The microdialysis data were analyzed using Friedman repeated measures analysis of variance on ranks with as post-hoc test Dunnett's method.

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Supporting Information Available: Elemental analyses for compounds **4**−**13** and **15**−**21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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