# Synthesis and Evaluation of a Set of 4-Phenylpiperidines and 4-Phenylpiperazines as D2 Receptor Ligands and the Discovery of the Dopaminergic Stabilizer 4-[3-(Methylsulfonyl)phenyl]-1-propylpiperidine (Huntexil, Pridopidine, ACR16)

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Modification of the partial dopamine type 2 receptor (D2) agonist 3-(1-benzylpiperidin-4-yl)phenol (**9a**) generated a series of novel functional D2 antagonists with fast-off kinetic properties. A representative of this series, pridopidine (4-[3-(methylsulfonyl)phenyl]-1-propylpiperidine; ACR16, **12b**), bound competitively with low affinity to D2 in vitro, without displaying properties essential for interaction with D2 in the inactive state, thereby allowing receptors to rapidly regain responsiveness. In vivo, neurochemical effects of **12b** were similar to those of D2 antagonists, and in a model of locomotor hyperactivity, **12b** dose-dependently reduced activity. In contrast to classic D2 antagonists, **12b** increased spontaneous locomotor activity in partly habituated animals. The "agonist-like" kinetic profile of **12b**, combined with its lack of intrinsic activity, induces a functional state-dependent D2 antagonism that can vary with local, real-time dopamine concentration fluctuations around distinct receptor populations. These properties may contribute to its unique "dopaminergic stabilizer" characteristics, differentiating **12b** from D2 antagonists and partial D2 agonists.

## Introduction

Dopamine type 2 receptors (D2) are primarily located in the basal ganglia of the mammalian brain but also occur in other structures of the brain, such as the cortex. The receptors, which are located at the neuronal membrane, belong to the monoamine subclass of the G-protein-coupled seven-transmembrane receptors (GPCRs).[1] In the brain, dopamine (**1**, Figure 1) exerts its action by means of synaptic as well as extrasynaptic release, affecting postsynaptic, presynaptic, and dendritic D2 receptor populations. Synaptic dopamine release is followed by fast reabsorption or degradation, processes that terminate D2 signaling. Drugs that interact with the agonist binding site of D2 receptors can be described as antagonists, partial agonists, or full agonists, and a number of these drugs have well-established applications in the treatment of various neurological and psychiatric disorders.

The affinity of a drug binding to its receptor is dependent on its association and dissociation rate constants, $k_{on}$ and $k_{off}$.[2] Commonly, medicinal chemistry optimization programs have generated high-affinity drugs with slow drug−receptor kinetics. Limited attention has been devoted toward optimizing D2 ligands with receptor kinetics comparable to those of natural dopamine signaling. It has been shown that dopamine D2 receptor kinetics differ among antipsychotic compounds, and it is proposed that fast-off kinetics (high $k_{off}$) is associated with less extrapyramidal side effect (EPS) liability,[3] probably because physiological responses to normal dopamine surges are possible.

Activation and G-protein coupling transform the D2 receptor to a state in which dopamine binds with higher affinity. Thus, the D2 receptor population is distributed between (i) a resting, low-affinity state ($D_2^{Low}$) and (ii) a catalytically active, high-affinity state ($D_2^{High}$).[4,5] The D2 agonists dopamine (**1**, Figure 1) and apomorphine (**2**, Figure 1) display high affinity in agonist ligand binding assays and induce a full catalytic reaction in functional assays (i.e., they have affinity and high intrinsic activity).[6−8] Dopamine D2 receptor partial agonists also generally bind with high affinity in such assays but are associated with less intrinsic activity than full agonists. Finally, dopamine D2 receptor antagonists, such as haloperidol (**3**, Figure 1) and olanzapine (**4**, Figure 1), bind with equal affinity in agonist and antagonist ligand binding assays[4,5,7] while essentially lacking intrinsic activity. The ratio of antagonist to agonist binding affinity $[K_i(D_2^{Low})/K_i(D_2^{High})]$ has thus been used as a measure of intrinsic activity.[6,9−11] It has been speculated that the main part of auto- and presynaptic receptors, which control the synthesis and release of dopamine, are of the dopamine $D_2^{High}$ affinity state. The postsynaptic receptors, on the other hand, are more equally distributed between the $D_2^{High}$ and $D_2^{Low}$ affinity states depending on the concentration of dopamine in the synapse. Further, it has been proposed that auto- and presynaptic receptors are sensitive to lower levels of endogenous dopamine than postsynaptic receptors. This difference in sensitivity to endogenous dopamine levels might explain why D2 partial agonists behave primarily as agonists at auto- and presynaptic receptors and as antagonists at postsynaptic receptors.[12]

Traditional dopamine D2 antagonists, such as haloperidol and olanzapine, are used to treat positive symptoms in schizophrenia and manic episodes in bipolar disorder.

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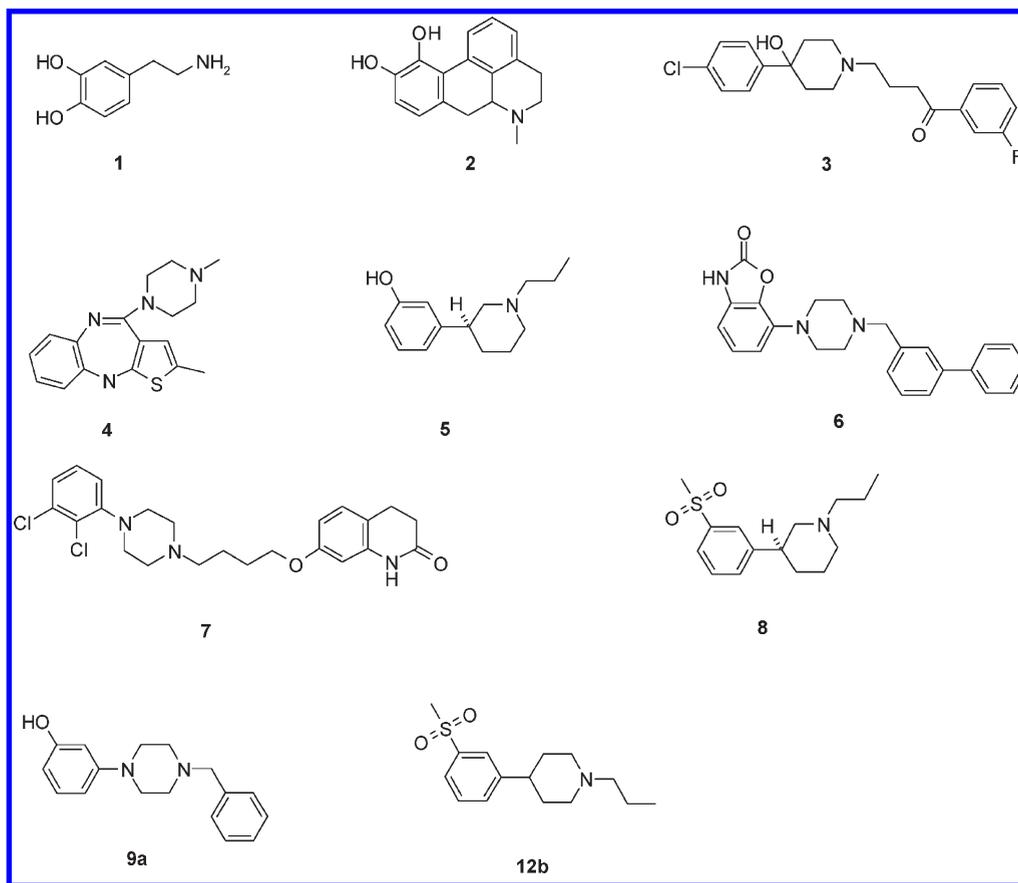
**Figure 1.** Dopamine D$_2$ ligands. Dopamine D$_2$ receptor agonists dopamine (**1**) and apomorphine (**2**), classical antagonists haloperidol (**3**) and olanzapine (**4**), partial agonists (−)-3-(3-hydroxyphenyl)-*N*-*n*-propylpiperidine (**5**), bifeprunox (**6**), aripiprazole (**7**), and 3-(1-benzylpiperidin-4-yl)phenol (**9a**), and dopaminergic stabilizers *S*-(−)-OSU6162 (**8**) and pridopidine (**12b**).

These compounds are associated with EPS, believed to occur as a result of excessive attenuation of brain dopamine neuronal activity due to the blockage of postsynaptic D$_2$ receptors.[13] The partial dopamine D$_2$ agonists, (−)-3-(3-hydroxyphenyl)-*N*-*n*-propylpiperidine ((−)-3PPP; **5**, Figure 1), bifeprunox (**6**, Figure 1) and aripiprazole (**7**, Figure 1) are effective in treating both the positive and negative symptoms of schizophrenia and have been reported to have a lower EPS liability than both typical and atypical antipsychotics.[13−15] Because of the low intrinsic activity of aripiprazole, it is thought to act as either a functional agonist or a functional antagonist, depending on the initial levels of dopamine; aripiprazole has been labeled a "dopamine system stabilizer".[16]

From a medicinal chemistry perspective, generally when the chemical properties of the agonists for a specific receptor system are compared with those of the corresponding antagonists, the agonists are relatively small molecules and hydrophilic in character, whereas the corresponding antagonists are usually larger and more lipophilic, lacking the essential pharmacophore elements for displaying agonist properties.[17−24] This general principle is illustrated by the two dopamine D$_2$ agonists dopamine and apomorphine (**1** and **2**, Figure 1), which have calculated log *P* (clog *P*)[25] values of 0.17 and 2.49, respectively, compared with the corresponding antagonists haloperidol and olanzapine (a structural analogue of clozapine) (**3** and **4**, Figure 1), which have clog *P* values of 4.45 and 4.51, respectively. The antagonists also lack certain essential pharmacophore elements, such as the catechol group and the basic nitrogen with the correct conformation and distance (i.e., phenethylamine) from the aromatic moiety.

The sites of interaction between agonists and the dopamine D$_2$ receptor have been characterized by mutagenesis studies in combination with three-dimensional homology modeling. This has revealed that Asp-118 on the third TM[*a*] helix is important for formation of a salt bridge with the protonated nitrogen, that serine residues in TM5 (Ser-193, Ser-194, and Ser-197) are important for formation of hydrogen bond interactions with the catechol function, and that a cluster of aromatic residues in TM4 and TM6 contribute to stabilization of the drug−receptor complex via hydrophobic interactions (mainly π−π stacking).[26−33] It has been proposed that TM6 undergoes a translational or rotational movement in the activation phase of GPCRs and that the interaction with an agonist facilitates this movement.[34−37] In line with this proposal, Goddard et al.[38] have speculated that interactions with TM3 (Asp-118) and TM5 (Ser-193 and Ser-197) by dopamine D$_2$ agonists pulls TM3 and TM5 closer together in the active state, allowing the flexible motion of TM6. By contrast, an antagonist (such as haloperidol) interacts strongly with TM helices 3 and 6 (having minimal contact with TM5), which therefore prevents such movement.[33,38] Interestingly, Goddard et al. have suggested that, in contrast to haloperidol,

clozapine binds to the agonist-binding pocket but lacks the tight interaction with serine residues on TM5 that is essential for the conformational changes necessary for intrinsic activity.[36] Thus, the more lipophilic antagonists seem to interact with hydrophobic residues in the binding pocket, which stabilizes the inactive state and prevents the optimal conformational changes as described above for agonists. Therefore, a useful approach in developing antagonists from agonist or partial agonist structures is to add a lipophilic system, such as a phenyl or cyclohexyl group, in a specific position on the agonist/partial agonist structure. This group could then interact with a hydrophobic part of the receptor system, preventing the receptor from undergoing the conformational changes needed for agonism.[22,23,39−42]

In the search for novel dopamine $D_2$ receptor antagonists, we have used a different approach, focusing on identifying the critical elements in $D_2$ agonists/partial agonists that are essential for intrinsic activity, under the hypothesis that a careful modification of the physicochemical properties of these elements would generate compounds with antagonistic properties (i.e., no intrinsic activity). The key to this approach was to maintain the chemical backbone of the agonist/partial agonist and performing the modification in such a way that the hydrophilicity either is retained or is even higher after the modification. We speculated that such modifications might lead to compounds that antagonize the actions of dopamine but, unlike lipophilic antagonists, lack the ability to stabilize the inactive state ($D_2^{Low}$) of the $D_2$ receptor. Further, we speculated that these compounds could exert modulatory effects on dopamine transmission and possibly state-dependent activity in vivo.

We have previously reported studies on a series of analogues to the 3-substituted phenylpiperidine **5**, one of the first reported partial $D_2$ agonists,[12,43] in which the validity of this approach was investigated. One of the key elements for the intrinsic activity of **5** has been shown to be a hydrogen bond donating/accepting phenolic OH group.[44] In a structure−activity relationship (SAR) study of these 3-substituted phenylpiperidines, we discovered that replacing the 3-OH group in **5** with electron-withdrawing groups rendered compounds with antagonistic properties at the dopamine $D_2$ receptor.[44,45] One of these compounds, **8** (Figure 1), has been found to display unique effects in vivo. Neurochemically, **8** displays effects similar to those of classic dopamine $D_2$ antagonists, such as an increase in synthesis and turnover of dopamine. However, in sharp contrast to the $D_2$ antagonists, **8** can stimulate, suppress, or show no effect on motor and behavioral symptoms, depending upon the prevailing dopaminergic tone. Therefore, the effects on motor and behavioral symptoms have been regarded as state dependent and **8** has been classified as a "dopaminergic stabilizer".[45−47] Thus, **8** represents a dopamine $D_2$ antagonist developed from a partial agonist, without the addition of lipophilic ring systems. It should be mentioned that **5** has a clog *P* of 3.18 whereas **8** has a clog *P* of 2.21. From in vitro binding studies, it has been shown that **8** more potently displaces an "agonist" from the $D_2^{High}$ binding site than an antagonist from the $D_2^{Low}$ binding site [a $K_i(D_2^{Low})/K_i(D_2^{High})$ ratio of 14 and 137 has been reported],[45,48] which would suggest that **8** has some intrinsic activity, and it has indeed been reported that **8** can have minor agonist effect at $D_2$ receptors in specially designed in vitro systems.[48,49] However, it has been clearly shown that **8** does not display any intrinsic activity in vivo, and therefore, the predictive value of these in vitro findings of intrinsic activity

**Table 1.** Compounds **9a−12b**
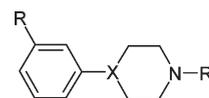


| compd | X | R | R′ |
|---|---|---|---|
| 9a | N | OH | benzyl |
| 9b | CH | OH | benzyl |
| 10a | N | OH | propyl |
| 10b | CH | OH | propyl |
| 11a | N | $SO_2Me$ | benzyl |
| 11b | CH | $SO_2Me$ | benzyl |
| 12a | N | $SO_2Me$ | propyl |
| 12b | CH | $SO_2Me$ | propyl |

requires further consideration.[45,47,50] The preference of dopaminergic stabilizers, such as **8**, for the displacement of agonists rather than antagonists at dopamine $D_2$ receptors triggered us to investigate the ability of various ligands to inhibit the $D_2$ receptor at different dopamine concentrations. We have recently demonstrated that haloperidol and aripiprazole display insurmountable (noncompetitive) $D_2$ antagonism whereas compounds such as **8** display surmountable (competitive) $D_2$ antagonism.[50] The insurmountable antagonism mediated by haloperidol and aripiprazole strongly indicates that they induce a long-lasting interaction with dopamine $D_2$ receptors, preventing dopamine from binding to and activating the receptor. The dopaminergic stabilizer, **8**, displays surmountable antagonism of dopamine, since it lacks the physicochemical properties required to stabilize the inactive state. Dopaminergic stabilizers have also been shown to display fast dissociation from $D_2$ receptors, which is believed to allow the dopamine receptors to rapidly regain responsiveness to dopamine.[50] These differences regarding mode of action may result in the unique effects of dopaminergic stabilizers in vivo, which are not seen with $D_2$ antagonists, agonists, or partial agonists.
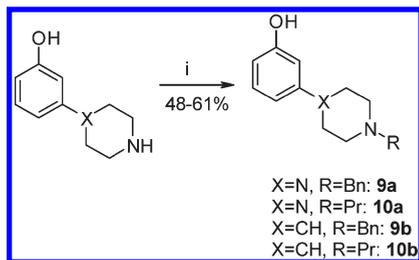
In the search for new chemical scaffolds to serve as starting points for the development of dopaminergic stabilizers, we have for the present study focused our attention on a series of dopamine $D_2$ partial agonists that were reported by Mewshaw and colleagues[51,52] including 3-(1-benzylpiperidin-4-yl)phenol (**9a**, Figure 1, Table 1). This compound has been shown to bind with high preference for the activated state of the $D_2$ receptor ($D_2^{High}$) and has been classified as a potential partial agonist based on the $K_i(D_2^{Low})/K_i(D_2^{High})$ ratio. We speculated that the key elements of **9a** responsible for its intrinsic activity were the phenol group, the anilinic nitrogen, and the large *N*-alkyl group and that modifications of these groups might lead to compounds with dopaminergic stabilizer properties. We herein present and discuss the synthesis and SAR, based on in vitro and in vivo data, of a series of novel compounds designed according to these principles. We also describe the receptor dissociation kinetics at the dopamine $D_2$ receptor of both these compounds and a set of known $D_2$ ligands.

## Chemistry

Compound **13** was synthesized from 1-bromo-3-methylthiobenzene by lithiation with *n*-butyllithium and quenching with N-substituted 4-piperidone (Scheme 1). Subsequent treatment with trifluoroacetic acid (TFA) in a $CH_2Cl_2$
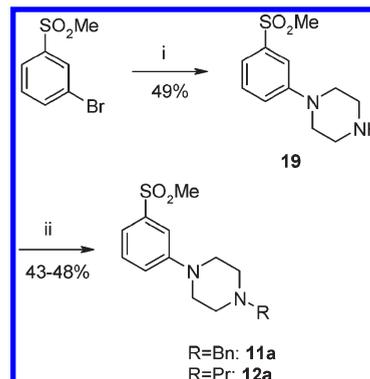
**Scheme 1.** Synthesis of Piperidines **11b** and **12b**[a]
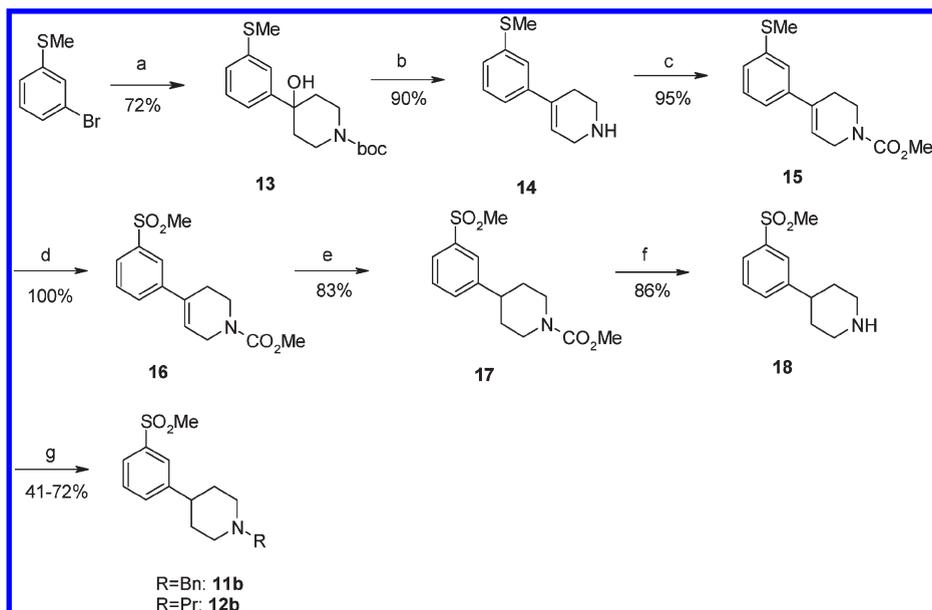


[a] Reagents and conditions: (a) *n*-butyllithium, 1-Boc-4-piperidone, THF; (b) trifluoroacetic acid, CH$_2$Cl$_2$, Δ; (c) triethylamine, methyl chloroformate, CH$_2$Cl$_2$; (d) *m*-CPBA, CH$_2$Cl$_2$; (e) Pd/C, H$_2$, MeOH, HCl; (f) HCl, EtOH, Δ; (g) RX, K$_2$CO$_3$, acetonitrile, Δ.

**Scheme 2.** Synthesis of Phenols **9a**−**10b**[a]



[a] Reagents and conditions: (i) RX, K$_2$CO$_3$, acetonitrile, Δ.

**Scheme 3.** Synthesis of Piperazines **11a** and **12a**[a]



[a] Reagents and conditions: (i) piperazine, NaO$^t$Bu, Pd$_2$(dba)$_3$, rac-BINAP, toluene, Δ; (ii) RX, K$_2$CO$_3$, acetonitrile, Δ.

solution gave **14** in excellent yield. Since sulfides contaminate the Pd in the catalyst used to reduce the piperidene double bond,[53] **14** was first protected by the addition of methyl chloroformate to afford the carbamate **15** and then quantitatively oxidized to the corresponding sulfone **16** using *m*-chloroperbenzoic acid (*m*-CPBA). The protection of the amine functionality was essential to avoid oxidation of the tetrahydropyridine to pyridine. The sulfone **16** was reduced with catalytic hydrogenation (Pd/C), affording the piperidine derivative **17** in good yield. After deprotection of **17** with aqueous HCl (8 M), the secondary amine **18** was treated with iodopropane and benzyl bromide, respectively, affording the desired products **11b** and **12b** in moderate to good yields (41−79%) (Scheme 1). Commercially available 3-(piperidin-4-yl)phenol was alkylated in the same manner, affording 3-(*N*-propyl-piperidin-4-yl)phenol (**10b**) and 3-(*N*-benzylpiperidin-4-yl)-phenol (**9b**, Scheme 2). Compound **19** (1-[3-(methylsulfonyl)-phenyl]piperazine) was afforded in moderate yield by C−N palladium-catalyzed cross-coupling of 1-bromo-3-(methylsulfonyl)benzene with piperazine using Pd$_2$(dba)$_3$ and rac-BI-NAP in toluene (Scheme 3). Reacting **19** or commercially available 1-(3-hydroxyphenyl)piperazine with iodopropane and benzyl bromide, respectively, afforded the alkylated piperazines **9a**, **10a**, **11a**, and **12a** in an average yield of 50% (Schemes 2 and 3).

**Results**

**In Vitro.** The agonists dopamine and apomorphine (**1** and **2**, respectively, Figure 1) bound with a strong preference to the agonist site (D$_2$$^{High}$) and possessed full intrinsic activity (Table 2). The classical D$_2$ antagonist, haloperidol (**3**), did not discriminate between the D$_2$$^{High}$ and D$_2$$^{Low}$ states, whereas olanzapine (**4**) seemed to have a slightly higher affinity for D$_2$$^{High}$ than for D$_2$$^{Low}$. The partial agonist (−)-3-PPP (**5**) bound with 130-fold higher affinity to D$_2$$^{High}$ than to D$_2$$^{Low}$ and displayed some, but not full, intrinsic activity (26% maximal efficacy [$E_{max}$]). Bifeprunox (**6**) had a binding ratio of only 2.5 but displayed an intrinsic activity ($E_{max}$ = 27%) similar to that of (−)-3-PPP in the functional assay. Aripiprazole (**7**) has previously been reported either to have a higher affinity for the agonist site than for the antagonist site[54] or to have similar affinity for both sites.[55] Our data support the findings of Tadori et al.[55] who reported that aripiprazole had no preference for D$_2$$^{High}$, but we found that the drug also displayed 11% intrinsic activity (Table 2). Results from our in vitro screening confirmed the binding profile previously

**Table 2.** LClogD, clog $P$, and in Vitro Data for Compounds **9a−12b** and Reference Compounds

| compd | LClogD[a] | clog $P$ | $D_2^{Low}$ $K_i$ (nM)[b] | $D_2^{High}$ $K_i$ (nM)[b] | $K_i^{Low}$/ $K_i^{High}$ | $E_{max}$[c] |
|---|---|---|---|---|---|---|
| **9a** | 4.93 | 3.21 | 115 (76−173) | 4.6 (3.7−5.7) | 25 | 36 ± 8 |
| **9b** | 3.93 | 3.91 | 285 (119−678) | 35 (28−43) | 8.1 | 0 |
| **10a** | 4.22 | 2.55 | 721 (424−1225) | 69 (49−97) | 10 | 0 |
| **10b** | 1.81 | 3.18 | 2570 (1270−5181) | 349 (278−438) | 7.3 | 0 |
| **11a** | 5.32 | 2.67 | 1923 (899−4113) | 431 (297−626) | 4.4 | 0 |
| **11b** | 4.39 | 2.94 | 841 (522−1355) | 392 (265−580) | 2.1 | 0 |
| **12a** | 3.19 | 2.00 | 1211 (766−1915) | 664 (498−886) | 1.8 | 0 |
| **12b** | 1.86 | 2.21 | 17550 (4588 − 67150) | 7521 (4057−13940) | 2.3 | 0[d] |
| dopamine (**1**) | NT | 0.17 | 2100 (1126−3919) | 2.9 (1.71−4.90) | 724 | 100[d] |
| apomorphine (**2**) | 3.43 | 2.49 | 244 (127−467) | 0.62 (0.49−0.79) | 393 | 91 ± 6[d] |
| haloperidol (**3**) | 4.45 | 3.85 | 1.9 (1.7−2.2) | 1 (0.7−1.4) | 1.9 | 0[d] |
| olanzapine (**4**) | 4.51 | 3.01 | 32 (17−62) | 6.1 (4.4−8.4) | 5.2 | NT |
| (−)-3PPP (**5**) | 1.91 | 3.33 | 2268 (1203−4278) | 17.4 (13−22) | 130 | 23 ± 8[d] |
| bifeprunox (**6**) | 6.59 | 4.78 | 0.1 (0.06−0.17) | 0.04 (0.03−0.06) | 2.5 | 28 ± 3[d] |
| aripiprazole (**7**) | 6.55 | 5.31 | 2.6 (2−3.2) | 2.8 (2−4.1) | 0.9 | 11 ± 2[d] |
| **8** | 2.22 | 2.36 | 3884 (2304−6545) | 755 (489−1166) | 5.1 | 0[d] |

[a] Calculated from liquid chromatography retention time. [b] Binding affinities (apparent $K_i$) of selected compounds to recombinant HEK-293 cells with [³H]spiperone as ligand for $D_2^{Low}$ and [³H]7-OH-DPAT for $D_2^{High}$ (95% confidence interval in parentheses). [c] Percentage of maximal efficacy ($E_{max}$) values on D2L-Gα$_{qi5}$ HEK293 cells,[50] $n$ = 3−4. NT: not tested. [d] Data from Dyhring et al.[50]
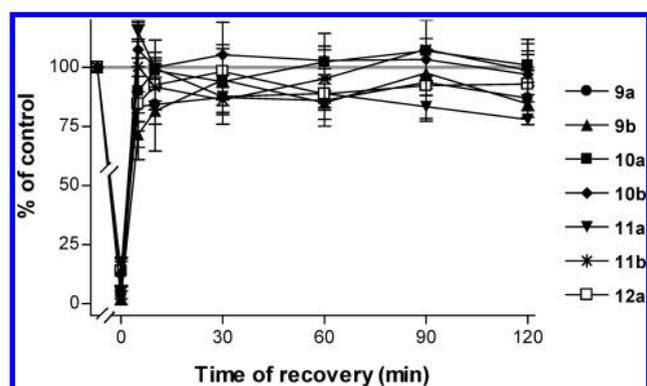


**Figure 2.** Recovery of dopamine $D_2$ receptor-mediated responsiveness after ligand washout. HEK-hD2L-Gα$_{qi5}$ cells were pretreated for 5 min with test compound, washed, and incubated for 5−120 min at room temperature. In order to ensure maximal receptor occupancies, high test compound concentrations (approximately 30-fold higher than the $EC_{50}/IC_{50}$ value) were used. After the recovery period, fluorescence responses were measured in response to 300 nM dopamine and normalized to the dopamine response in the absence of compound pretreatment (presented as a gray line at 100%). Data points represent the mean ± SEM, $n$ = 3−4.

reported by Mewshaw et al. for compound **9a** (Table 2; $K_i(D_2^{High})$ = 4.6 nM, $K_i(D_2^{Low})$ = 115 nM).[52] In addition, **9a** displayed partial agonist activity in the functional assay, with an efficacy of 36%. Chemical modifications of **9a** produced a group of compounds (**9b−12b**) with lower affinity for both $D_2^{High}$ and $D_2^{Low}$ but with a consistent preference for the agonist site ($D_2^{High}$, Table 2). However, none of these compounds displayed any detectable intrinsic activity in the functional in vitro assay (Table 2), in the case of **12b** consistent with previous reports.[47,56] Regarding receptor kinetics, compounds **9a−12b** all displayed fast dissociation from the dopamine $D_2$ receptor as shown in Figure 2 and as reported by Dyhring et al.[50]

The $D_2$ recovery rates measured for these compounds were similar to that of dopamine and in sharp contrast to those of classic antagonists, such as haloperidol, and partial agonists, such as aripiprazole and bifeprunox. The atypical antipsychotic olanzapine on the other hand has been shown to display a moderate dissociation rate.[50]

**In Vivo.** The dopamine agonist, apomorphine, induced a dose-dependent reduction in tissue levels of DOPAC in the
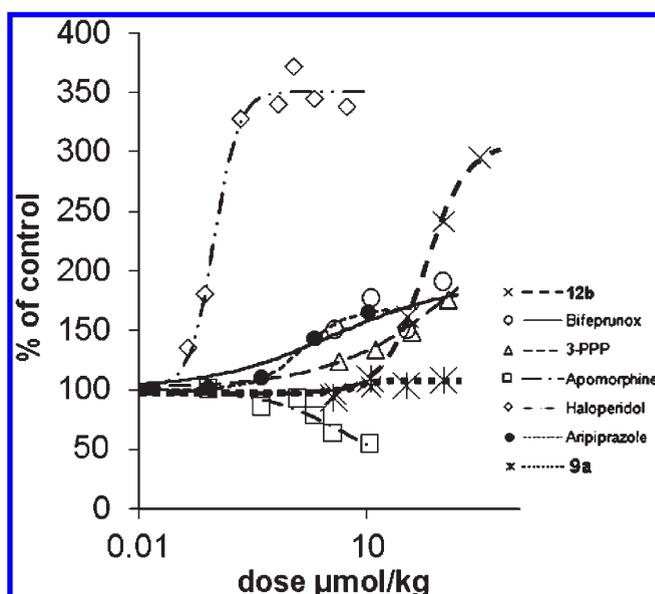


**Figure 3.** Dose-dependent effects of **12b** and several dopamine $D_2$ agonists, antagonists, and partial agonists on DOPAC levels in the striatum.

striatum (Figure 3 and Table 3) and a pronounced increase in LMA in partly habituated rats, whereas the classic dopamine $D_2$ antagonists, haloperidol and olanzapine, induced substantial increases in DOPAC levels (∼360−420% of control levels) along with strong (haloperidol) to moderate (olanzapine) reductions in LMA (Figure 3 and Table 3). The partial agonists (−)-3-PPP, aripiprazole, and bifeprunox induced a dose-dependent, partial increase in DOPAC levels relative to haloperidol/olanazapine (∼150−175% of control levels, Figure 3). In addition, aripiprazole and bifeprunox induced a strong reduction in spontaneous LMA in partly habituated rats, whereas (−)-3-PPP induced only a mild reduction (Table 3). The antagonists and partial agonists were also effective in decreasing amphetamine-induced hyperlocomotion (Table 3). In contrast to the agonists, partial agonists, and antagonists described above, the dopaminergic stabilizer **8** generated an increase in DOPAC levels comparable to that seen with classic antagonists but,

**Table 3.** In Vivo Data for Compounds **9a**−**12b** and Reference Compounds

| compd | DOPAC, % of control ± SEM[a] | LMA, % of control ± SEM[b] | LMA, % of amphetamine ± SEM[c] |
|---|---|---|---|
| **9a** | $108 \pm 4^d$ | $8 \pm 2^d$ | $10 \pm 2^{d,m}$ |
| **9b** | $317 \pm 13^{e,m}$ | $85 \pm 25^e$ | $12 \pm 1^{e,m}$ |
| **10a** | $261 \pm 39^{e,m}$ | $31 \pm 3^e$ | $16 \pm 1^{e,m}$ |
| **11a** | $248 \pm 10^{d,m}$ | $17 \pm 9^d$ | $15 \pm 4^{d,m}$ |
| **11b** | $310 \pm 16^{e,m}$ | $44 \pm 3^e$ | $6 \pm 2^{f,m}$ |
| **12a** | $310 \pm 16^{e,m}$ | $27 \pm 9^e$ | $6 \pm 1^{e,m}$ |
| **12b** | $265 \pm 10^{d,m}$ | $262 \pm 28^{d,m}$ | $12 \pm 3^{g,m}$ |
| apomorphine (**2**) | $77 \pm 3^{h,m}$ | $7118 \pm 779^{h,m}$ | NT |
| haloperidol (**3**) | $425 \pm 3^{i,m}$ | $7 \pm 4^i$ | $1 \pm 0^{i,m}$ |
| olanzapine (**4**) | $362 \pm 5^{j,m}$ | $17 \pm 5^{j,m}$ | $6 \pm 2^{j,m}$ |
| (−)-3PPP (**5**) | $175 \pm 8^{k,m}$ | $37 \pm 17^k$ | NT |
| bifeprunox (**6**) | $152 \pm 12^{l,m}$ | $7 \pm 2^{l,m}$ | $5 \pm 3^{l,m}$ |
| aripiprazole (**7**) | $150 \pm 3^{l,m}$ | $2 \pm 1^{l,m}$ | $9 \pm 1^{l,m}$ |
| **8** | $260 \pm 15^{d,m}$ | $215 \pm 62^d$ | $37 \pm 14^d$ |

[a] Post-mortem biochemistry of levels of DOPAC in the striatum compared to saline control ($n = 4$). [b] LMA during 15−60 min after injection measured at 25 Hz compared to saline control. [c] LMA during 15−60 min after injection measured at 25 Hz compared to amphetamine (1.5 mg/kg intraperitoneally) pretreated rats ($n = 4$). To compare the in vivo effects of the different compounds, the lowest dose required to produce a maximal DOPAC response was selected. NT: not tested. [d] 100 $\mu$mol/kg. [e] 33 $\mu$mol/kg. [f] 50 $\mu$mol/kg. [g] 150 $\mu$mol/kg. [h] 6.59 $\mu$mol/kg (2 mg/kg). [i] 1.0 $\mu$mol/kg (0.37 mg/kg). [j] 10.5 $\mu$mol/kg (3.3 mg/kg). [k] 117 $\mu$mol/kg (30 mg/kg). [l] 7.68 $\mu$mol/kg (3.7 mg/kg). [l] 4.46 $\mu$mol/kg (2 mg/kg). [m] $P < 0.05$ using Student's $t$ test.

in contrast to classic antagonists, increased spontaneous LMA in partly habituated rats. However, **8** still reduced LMA in amphetamine-pretreated animals at doses equivalent to those that increased spontaneous activity in partly habituated rats (Table 3).

The partial agonist **9a** had no influence on DOPAC levels but induced a strong reduction in LMA in normal rats. With the exception of **10b**, which was not tested, compounds **9b**−**12b** all generated a dose-dependent increase in DOPAC levels (250−300% of control) while inducing moderate decreases (**10a**, **11a**, **11b**, **12a**), minor decreases (**9b**) or, in an extreme case, increases (**12b**) in LMA in partly habituated rats. The increase in LMA displayed by **12b** was similar to that of **8**. Compounds **9a**−**12b** where all effective in decreasing amphetamine-induced hyperlocomotion (Table 3), with the exception of **10b** (not tested).

## Discussion

As reported by other authors, the affinity ratio between $D_2^{High}$ and $D_2^{Low}$ correlates positively with the degree of intrinsic activity. In the current study, agonists, such as dopamine and apomorphine, bound with strong preference to the agonist site ($D_2^{High}$) and displayed full intrinsic activity in the functional assay; in contrast, partial agonists exhibited intermediate $D_2^{High}/D_2^{Low}$ ratios and had lower efficacy in the functional assay. The classic dopamine $D_2$ antagonist, haloperidol, bound with high affinity to both sites and displayed no intrinsic activity. However, olanzapine was found to differentiate between the two sites, showing a 5.2-fold higher affinity for $D_2^{High}$ over $D_2^{low}$. This finding is in line with the modeling results of Goddard et al., which show that members of the dibenzodiazepine class (exemplified by clozapine) bind preferentially to the dopamine agonist pocket, although they are unable to engender the conformational changes seen with agonists because of the proposed weaker binding to serine residues on TM5.[38]

The binding properties of the lead compound, **9a**, reported by Mewshaw et al. to be a partial agonist,[52] were confirmed, and an intrinsic activity of 36% further supports its classification as a partial agonist. In addition, **9a** was found to display surmountable $D_2$ antagonism against dopamine (competitive effect) and fast receptor dissociation kinetics in vitro. All structural modifications of **9a** made in the present study (**9b**−**12b**; Tables 1 and 2) resulted in compounds with no intrinsic activity but with a consistent binding preference for $D_2^{High}$, albeit less pronounced than that of **9a**, indicating that all the structural elements in **9a** (phenol, piperazine, and *N*-benzyl) are required for intrinsic activity at the $D_2$ receptor. These findings are in contrast to the 3-substituted phenylpiperidines (e.g., **5** (3-PPP)), which can accept a larger variation in substitution pattern on the aromatic ring and the basic nitrogen while maintaining high intrinsic activity.[45,57] This indicates that the lack of phenethylamine backbone in the **9a** series leads to a structural class less prone to induce intrinsic activity, and therefore, additional interactions are needed. In addition, compounds **9b**−**12b** were found to display surmountable $D_2$ antagonism with fast dissociation from the dopamine $D_2$ receptor (Table 2 and Figure 2), findings in line with what we would expect from these compounds as a result of the similarity to the agonist chemical motif and their high hydrophilicity.

From a SAR perspective, it is interesting to note the loss of intrinsic activity when exchanging the piperazine ring of **9a** to a piperidine ring (**9b**). This effect may be related to a more preferred conformation of **9a** compared to **9b**; piperazines are known to be coplanar between the piperazine ring and the aromatic ring as the most stable conformation due to sp$^2$ hybridization on the anilinic nitrogen. However, for the piperidines the most stable conformation is when the piperidine ring and the aromatic ring are perpendicular to each other.[58,59] Other differences that may influence the intrinsic activity are the lower p$K_a$ for the piperazines as well as the character of the $\pi$-system, since the anilinic nitrogen will be partly delocalized. It is also interesting to note that the 3-hydroxy isomers were generally found to bind with higher affinity to both $D_2^{High}$ and $D_2^{Low}$ than the corresponding 3-methylsulfone isomers. Furthermore, when **9a** was compared with **11a**, the intrinsic activity was lost, suggesting that even though a sulfone group can participate in hydrogen bonding with the hydroxy groups on the dopamine $D_2$ receptor (i.e., serine groups on TM5[33]), this interaction seems to be less optimal than for the corresponding hydroxy group. Regarding the *N*-alkyl group, the lack of intrinsic activity of the propyl (**10a**) compared with the benzyl (**9a**) indicates that in this series the additional aromatic ring system stabilizes the high affinity state needed for a functional response.

Lipophilicity often contributes to binding affinity, and in order to investigate this relation, we plotted clog *P* values for the entire set of compounds in Table 2 against the $K_i$ for $D_2^{Low}$ and $D_2^{High}$ (excluding dopamine). As shown in Figure 4, there was a clear relationship between clog *P* and affinity for $D_2^{Low}$, indicating that lipophilicity is a factor that contributes to affinity for dopamine $D_2$ receptors in the inactivated state and suggesting that such affinity is driven by hydrophobic interactions with hydrophobic residues in the dopamine $D_2$ receptor. A similar approach for $D_2^{High}$ gave a poor correlation ($R^2 = 0.43$), which may indicate that more specific interactions, rather than hydrophobic interactions, may be relevant for agonists and partial agonists. It is also interesting to note that in the range of lipophilicity and affinity values
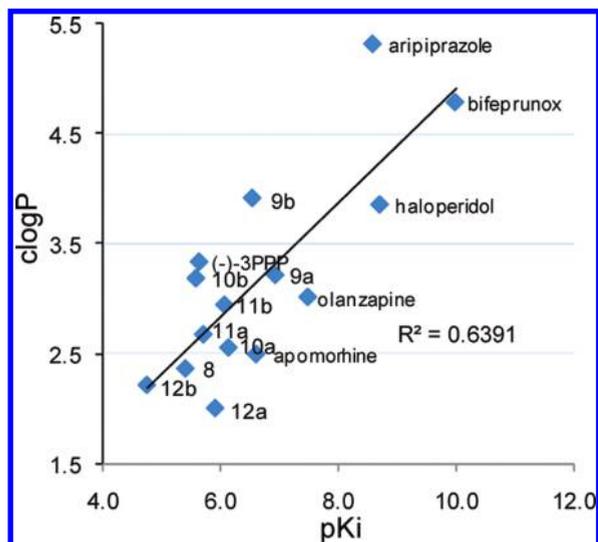
**Figure 4.** Relationship between binding affinities (apparent $K_i$ of selected compounds to recombinant HEK-293 cells using [$^3$H]spiperone as a ligand) (p$K_i$) and calculated log $P$ values (clog $P$).

demonstrated for compounds **9b**−**12b**, the attributes of surmountable antagonism and fast off kinetics are pervasive. Although such a profile might be anticipated to be a product of low affinity, compounds **9a** and **9b** both have high affinity and demonstrate surmountable antagonism and fast off kinetics. Further, we have previously demonstrated that the compound *N*-{[(2*S*)-5-chloro-7-(methylsulfonyl)-2,3-dihydro-1,4-benzodioxin-2-yl]methyl}ethanamine (NS30678), which is equipotent with haloperidol in vitro, also displays this profile.[50] Thus, the surmountable antagonism property is most probably related to the mode of interaction rather than a mere low-affinity phenomenon.

Another trend in the data set (i.e., **9a**−**12b**) is that the piperazines bind with higher affinity to the D$_2$ receptors than the corresponding piperidines, with the exception of compounds **11a** and **11b** (Table 2). Even though the piperidines are more lipophilic than the piperazines when comparing clog $P$ (3.21 for **9a**, 3.91 for **9b**, 2.55 for **10a**, 3.18 for **10b**), we speculated whether this is relevant under physiological conditions. HPLC is a useful method for comparing the lipophilicity of a range of compounds.[60,61] We therefore decided to compare the compounds in a reverse-phase HPLC system using a water mobile phase at pH 7.4. From the retention time we then calculated LClogD values for each compound, and the results clearly show that the piperazines are more lipophilic than the piperidines (shown as higher LClogD values for the piperazines; Table 2), which may explain their generally higher binding affinities. The higher LClogD lipophilicity of the arylpiperazines compared with the piperidines is probably explained by the differences in p$K_a$ of the basic nitrogen. Arylpiperazines display a p$K_a$ of ∼6.0−7.5 compared with ∼8.0−9.5 for the piperidines,[62,63] leading to a higher level of ionization of the arylpiperidines than of the arylpiperazines at physiological pH.

By using in vivo data, we can easily discriminate between agonists, partial agonists, and antagonists. The typical in vivo profile demonstrated by a full D$_2$ agonist is a dose-dependent reduction in tissue levels of dopamine metabolites (DOPAC and HVA), as shown in Figure 3, plus a pronounced increase in LMA at high doses (Table 3). The decrease in dopamine metabolites has been regarded as a consequence of the stimulation of the presynaptic D$_2$ receptors controlling the synthesis

and release of dopamine and its metabolites into the synapse, whereas the increase in behavioral activity has been regarded as a consequence of the stimulation of postsynaptic D$_2$ receptors. The opposite effect, with a dose-dependent increase in dopamine metabolites, reaching a maximum level of approximately 350% of control levels (Figure 3), and a strong reduction in LMA (Table 3), was seen with haloperidol, whereas olanzapine induced a moderate reduction in LMA. The efficacy on dopamine metabolites was lower with the partial agonists aripiprazole, (−)-3PPP, and bifeprunox, engendering maximal DOPAC levels of 150−175% of control levels (Figure 3). Thus, levels of DOPAC correlated negatively with the level of intrinsic activity (Tables 2 and 3) for agonists, partial agonists, and antagonists. The partial agonists, much like the antagonists haloperidol and olanzapine, also induced a reduction in LMA (Table 3). Compound **9a**, which had a relatively high intrinsic activity in the functional in vitro assay, was found to be neutral on DOPAC levels but potently reduced spontaneous LMA. This result indicates that **9a** has a higher intrinsic activity in vivo than the partial agonists (−)-3-PPP, bifeprunox, and aripiprazole, as determined by the functional in vitro assay.

In contrast to the partial agonist **9a**, compounds **9b**−**12b** lacked intrinsic activity and induced a dose-dependent increase in DOPAC levels similar to that seen with the full D$_2$ antagonists haloperidol and olanzapine (Table 3). Despite this consistent dopamine D$_2$ antagonist neurochemical profile, compounds **9b**−**12b** displayed a range of effects on spontaneous LMA in rats with low psychomotor activity. Some compounds, such as **11a** and **12a**, potently inhibited LMA, in line with what would be predicted from the neurochemical effects of these compounds (i.e., a maximal increase in DOPAC levels). However, compound **12b** induced an increase in LMA but still behaved as a dopamine D$_2$ antagonist in that it increased DOPAC levels with full efficacy. These effects were similar to those of the dopaminergic stabilizer, **8**, and are consistent with results reported by others.[45,47,64] Independent of the effects on spontaneous LMA (ranging from stimulation to reduction), all compounds were effective in blocking amphetamine-induced hyperactivity (Table 3).

However, it is not fully explained how compounds that all behave as antagonists at D$_2$ receptors, based on their effect on dopamine neurochemistry (i.e., an increase in DOPAC levels), can induce different effects on behavioral activity in partly habituated rats. For clarification, the dose at which we measured behavioral activity is the dose at which a compound reaches its maximal effect on DOPAC levels. From the data in Tables 2 and 3 we found, not surprisingly but very interestingly, a clear correlation between the affinity for D$_2$$^{Low}$ receptors and the effects on LMA in vivo (Figure 5; $R^2 = 0.62$ for D$_2$$^{Low}$). A similar correlation was also seen for the D$_2$$^{High}$ receptors ($R^2 = 0.59$; the agonist apomorphine was excluded). These results indicate that the inhibitory effect on spontaneous LMA is driven mainly by affinity for the dopamine D$_2$ receptors (either D$_2$$^{High}$ or D$_2$$^{Low}$), independent of whether the compound is a partial D$_2$ agonist or a compound with D$_2$ antagonist properties, such as **9b**−**12b**, haloperidol, or olanzapine. Behavioral activity is known to be influenced by effects on postsynaptic dopamine D$_2$ receptors, and therefore, the reduction in LMA is thought to be a consequence of the displacement of dopamine and the blockade of postsynaptic D$_2$ receptors. This also suggests that the partial agonists aripiprazole, bifeprunox, and compound **9a** exert their potent reduction of motor activity by the blockade of postsynaptic D$_2$ receptors.
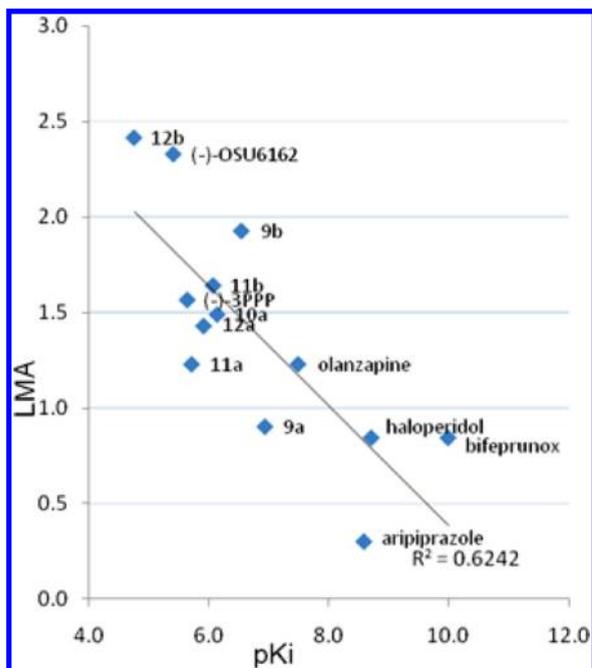
**Figure 5.** Relationship between binding affinities (apparent $K_i$ of selected compounds to recombinant HEK-293 cells using [³H]spiperone as a ligand) ($pK_i$) and the logarithm of locomotor activity expressed as a percentage of control levels (LMA).
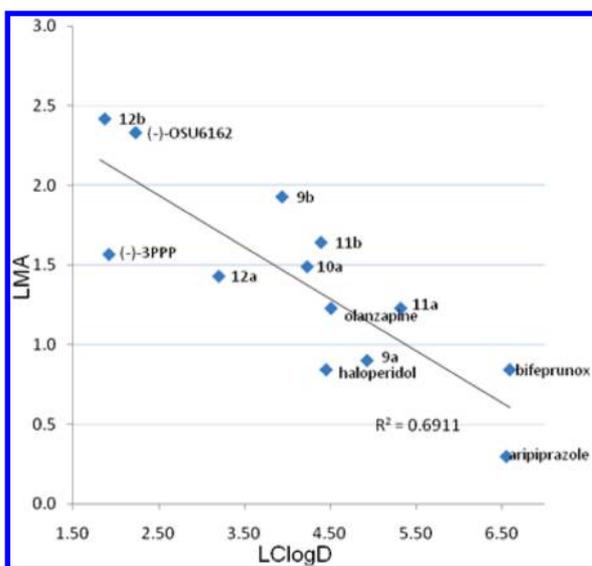


**Figure 6.** Relationship between LClogD (as previously described) and the logarithm of locomotor activity expressed as a percentage of control levels (LMA).

It must be emphasized that effects on other receptor systems could contribute to the influence on motor activity.

In addition to in vitro affinity, it is also interesting to note that there was a strong correlation between spontaneous motor activity and the lipophilicity of the compounds ($R^2 = 0.69$; Figure 6). This again indicates that potency and efficacy for $D_2$ antagonism, and thereby reduction in spontaneous LMA, are mainly driven by hydrophobic interactions stabilizing the $D_2^{Low}$ state. However, as displayed by **12b**, it seems that by reduction of lipophilicity, it is possible to retain the effects on dopaminergic neurochemistry (i.e., an increase in DOPAC levels), while the inhibitory effects on spontaneous

LMA are diminished. From an SAR perspective, it is interesting to note that the more lipophilic piperazines, **9a**, **11a** and **12a**, induced a stronger reduction in spontaneous LMA in the partly habituated animals than the corresponding piperidines, **9b**, **11b**, and **12b**. The possible difference in pharmacokinetic and pharmacodynamic properties can be a concern when plotting in vivo against in vitro data. However, all compounds are given subcutaneously to avoid first-pass metabolism and the most polar compound in this series, **12b**, has a brain/plasma ratio of 3 (unpublished results) and a pronounced effect on dopamine release and turnover. This supports the assumption that penetration of the blood−brain barrier is not an issue within this series. Furthermore, the effects of pharmacokinetic differences between the compounds are minimized by studying LMA effects at doses where maximal DOPAC response is achieved.

One of the hallmarks for dopaminergic stabilizers, such as **12b** is that it can increase behavioral activity in animals with low baseline activity (partly habituated animals) despite having full $D_2$ antagonist effects on dopamine synthesis and metabolism and inhibitory effects on psychostimulant induced behavioral hyperactivity. Differences in extrasynaptic versus synaptic dopamine neurotransmission,[65] partial dopamine receptor agonism,[48,66] and the interaction with both an allosteric and orthosteric site on the dopamine $D_2$ receptor, resulting in an increased response to dopamine and an antagonizing dopamine action,[49,64] have all been proposed as mechanisms by which these compounds exert their effects. Here, we have demonstrated that dopaminergic stabilizers display unique effects in vitro, such as surmountable antagonism and fast-off kinetics, without intrinsic activity, which differ from those of classical $D_2$ antagonists and partial agonists.[56] We have also shown that a low affinity for $D_2$ receptors is a prerequisite for an increase in behavioral activity (Figure 5) among the compounds investigated. As **8** and **12b** both induced a dose-dependent increase in dopamine and dopamine metabolites (DOPAC) in the striatum, cortex, and limbic areas, this indicates that these molecules must interact with $D_2$ autoreceptors, competing with dopamine and leading to an increase in the synthesis and metabolism of dopamine. The low affinity and rapid dissociation allow for some fluctuation in the degree of activation of postsynaptic $D_2$ receptors in response to endogenous dopamine surges and, thereby, do not completely attenuate physiological neurotransmission. We propose that as affinity increases, the postsynaptic $D_2$ blockade becomes more pronounced and a clear reduction in behavioral activity is seen (Figure 5). **8** and **12b** appear to exhibit surmountable $D_2$ antagonism and low affinity and act as state-dependent $D_2$ antagonists, allowing for either an increase in spontaneous LMA or a decrease in hyperactivity states, such as that engendered by D-amphetamine.

**Conclusions**

We have shown that starting from a novel dopamine $D_2$ partial agonist such as **9a**, the modification of physicochemical properties important for intrinsic activity can lead to the development of pure dopamine $D_2$ antagonists. By reduction of the lipophilicity and thereby reduction of the affinity for $D_2$ receptors, compounds with state-dependent effects on LMA are obtainable. This has led to the discovery of the dopaminergic stabilizer, **12b**. It has been shown that this compound displays surmountable $D_2$ antagonism with fast dissociation, and on the basis of the chemical motif, we suggest that the mode of interaction is similar to that of dopamine $D_2$ agonists but

that it lacks essential pharmacophore elements needed for intrinsic activity and, in addition, lacks the ability to stabilize the inactive state of the $D_2$ receptor. In conclusion, **12b** has a profile of low lipophilicity, low affinity, surmountable antagonism, and fast receptor dissociation. This permits it to compete with dopamine in such a way that state-dependent antagonism of $D_2$ receptor function is attainable while still allowing attenuated physiological neurotransmission to persist.

This action profile, reflected in vivo by, for example, efficacy in models of behavioral hyperactivity combined with a lack of inhibitory motor effects in the normal state, may be therapeutically useful in the treatment of CNS disorder related to disturbed activity in central dopaminergic pathways, such as movement disorders and schizophrenia.

### Experimental Section

**Chemistry General.** $^1$H and $^{13}$C NMR spectra were recorded in MeOH-$d_6$ or CDCl$_3$ at 300 and 75 MHz, respectively, using a Varian XL 300 spectrometer, or at 400 and 100 MHz, respectively, using a Mercury Plus 400 spectrometer. Chemical shifts are reported as $\delta$ values (ppm) relative to an internal standard (tetramethylsilane). Low-resolution mass spectra were recorded on a HP 5970A instrument operating at an ionization potential of 70 eV. The mass detector was interfaced with a HP5700 gas chromatograph equipped with a fused silica column (11 m, 0.22 mm i.d.) coated with cross-linked SE-54 (film thickness 0.3 mm, He gas, flow 40 cm/s). Elemental analyses were performed by MikroKemi AB, Uppsala, Sweden. Melting points were determined with a point microscope (Reichert Thermovar) and are uncorrected. For flash chromatography, silica gel 60 (0.040−0.063 mm, VWR, no. 109385) was used. The amine products were converted to the corresponding salts by dissolving the free base in EtOH and adding 1 equiv of the acid (fumaric or oxalic) or ethanolic HCl solution. The solvent was removed and azeotroped with absolute EtOH in vacuo followed by recrystallization from appropriate solvents. Purity of all target compounds where assessed as greater than 95% by elemental analysis (C, H, N).

**Detailed Synthetic Procedures. 1-*tert*-Butoxycarbonyl-4-hydroxy-4-[3-(methylthio)phenyl]piperidine (13).** To a solution of 3-bromothioanisole (4.25 g, 20.9 mmol) in dry THF (30 mL) at −78 °C was added *n*-butyllithium in hexane (2.5 M, 9.3 mL, 23.2 mmol). The mixture was stirred at −78 °C under an N$_2$ atmosphere for 30 min and then allowed to warm to −20 °C for 2 min. After the mixture was again cooled to −78 °C, 1-Boc-4-piperidone (4.38 g, 22.0 mmol) in dry THF (20 mL) was added via syringe. The solution was allowed to warm to 20 °C and stirred for an additional 10 min. The reaction mixture was then diluted with aqueous NH$_4$Cl, and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 × 50 mL) and the combined organic phase was washed with brine, dried (MgSO$_4$), and concentrated in vacuo to give 6.8 g of crude product. The residue was purified by flash chromatography using CH$_2$Cl$_2$/MeOH [19:1 (v/v)] as eluent, affording **13** as a gum (4.9 g, 72%). MS *m/z* (relative intensity, 70 eV) 323 (M$^+$, 10), 267 (17), 178 (12), 57 (bp), 56 (15). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.83 (s, 9 H), 2.05 (d, $J$ = 12.4 Hz, 4 H), 2.23−2.40 (m, 2H), 2.84 (s, 3H), 3.57 (t, $J$ = 12.0 Hz, 2H), 4.37 (br s, 1H), 7.50 (d, $J$ = 7.3 Hz, 1H), 7.55 (d, $J$ = 1.5 Hz, 2H), 7.62 (d, $J$ = 7.6 Hz, 1H), 7.74 (d, $J$ = 1.5 Hz, 1H).

**4-[3-(Methylthio)phenyl]-1,2,3,6-tetrahydropyridine (14).** To a solution of **13** (10.1 g, 31.2 mmol) in CH$_2$Cl$_2$ (250 mL) was added TFA (70 mL), and the mixture was refluxed for 48 h. After cooling, the reaction mixture was poured onto NaOH (5 M, 150 mL) and the phases were separated. The aqueous phase was extracted with CH$_2$Cl$_2$ (3 × 50 mL), and the combined organic phase was washed with brine, dried (MgSO$_4$), and concentrated in vacuo to give 5.77 g (90%) of **14**. MS *m/z* (relative intensity,

70 eV) 205 (M$^+$, 73), 158 (44), 129 (95), 128 (80), 82 (bp). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 2.54 (s, 3H), 2.55−2.60 (m, 2H), 3.18−3.24 (m, 2H), 3.51−3.58 (m, 1H), 3.64 (m, 2H), 6.14−6.18 (m, 1H), 7.17−7.24 (m, 2H), 7.27−7.34 (m, 2H).

**1-Methoxycarbonyl-4-[3-(methylthio)phenyl]-1,2,3,6-tetrahydropyridine (15).** To a solution of **14** (6.1 g, 29.7 mmol) and triethylamine (5.39 mL, 35.7 mmol) in CH$_2$Cl$_2$ (200 mL) at 0 °C was added methyl chloroformate (2.53 mL, 32.7 mmol) in CH$_2$Cl$_2$ (50 mL), and the reaction mixture was stirred for 2 h. Aqueous Na$_2$CO$_3$ (10%, 100 mL) was added, and the phases were separated. The aqueous phase was extracted with CH$_2$Cl$_2$ (3 × 50 mL), and the combined organic phase was washed with brine, dried (MgSO$_4$), and concentrated in vacuo to give 8.1 g of crude product. The residue was purified by flash chromatography using isooctane/ethyl acetate [1:1 (v/v)] as eluent, affording pure **15** (7.4 g, 95%). MS *m/z* (relative intensity, 70 eV) 263 (M$^+$, 45), 248 (89), 129 (83), 128 (bp), 59 (96). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ ppm 2.49 (s, 3 H), 2.73 (s, 1 H), 3.64−3.71 (m, 2 H), 3.74 (s, 3 H), 3.77−3.84 (m, 1 H), 4.11 (s, 2 H), 6.05 (s, 1 H), 7.14 (t, $J$ = 7.7 Hz, 2 H), 7.23−7.29 (m, 2 H).

**1-Methoxycarbonyl-4-[3-(methylsulfonyl)phenyl]-1,2,3,6-tetrahydropyridine (16).** A solution of **15** (6.28 g, 23.87 mmol) in CH$_2$Cl$_2$ (300 mL) was cooled to 0 °C, and *m*-CPBA (12.2 g, 52.5 mmol) was added in portions over a period of 30 min. The mixture was stirred at 0 °C for 1.5 h and then at ambient temperature for 1 h. Aqueous Na$_2$CO$_3$ (10%, 100 mL) was added, and the phases were separated. The aqueous phase was extracted with CH$_2$Cl$_2$ (3 × 50 mL) and the combined organic phase was washed with brine, dried (MgSO$_4$), and concentrated in vacuo to give 8.6 g of crude product that was used in the subsequent step without any further purification. MS *m/z* (relative intensity, 70 eV) 295 (M$^+$, 19), 280 (56), 129 (70), 128 (89), 59 (bp).

**1-Methoxycarbonyl-4-[3-(methylsulfonyl)phenyl]piperidine (17).** To a solution of **16** (8.06 g, 27.3 mmol) in MeOH (160 mL) was added concentrated HCl (8 mL) and Pd/C (1.5 g) under N$_2$, and the reaction mixture was hydrogenated under H$_2$ (50 psi) for 15 h. Filtration through Celite and evaporation of the filtrate afforded 8.6 g of crude product as the HCl salt. Purification with flash chromatography using CH$_2$Cl$_2$/MeOH [30:1 (v/v)] as eluent afforded pure **17** (6.73 g, 83%). MS *m/z* (relative intensity, 70 eV) 297 (M$^+$, 54), 282 (62), 238 (bp), 115 (92), 56 (93). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.58−1.77 (m, 2 H), 1.79−1.89 (m, 2 H), 2.62−2.81 (m, 3 H), 3.07−3.16 (m, 5 H), 7.52−7.61 (m, 2 H), 7.76−7.87 (m, 2 H).

**4-[3-(Methylsulfonyl)phenyl]piperidine (18).** To a solution of **17** (5.1 g, 17.2 mmol) in absolute EtOH (40 mL), HCl (8 M, 100 mL) was added. The mixture was refluxed for 24 h. The EtOH was evaporated, and the aqueous phase was made basic with NaOH (5 M). The aqueous phase was extracted with ethyl acetate (3 × 50 mL) and the combined organic phase was washed with brine, dried (MgSO$_4$), concentrated in vacuo, and purified by flash chromatography using ethyl acetate/MeOH [1:1 (v/v)] as eluent to give 3.5 g (86%) of **18**. MS *m/z* (relative intensity, 70 eV) 239 (M+, 59), 238 (50), 69 (20), 57 (79), 56 (bp). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ ppm 1.66 (dd, $J$ = 12.6, 4.20 Hz, 2 H), 1.85 (s, 2 H), 2.78−2.93 (m, 3 H), 3.06 (s, 3 H), 3.73 (s, 3 H), 7.44−7.57 (m, 2 H), 7.71−7.85 (m, 2 H).

**4-[3-(Methylsulfonyl)phenyl]-1-propylpiperidine (12b).** Compound **18** (3.5 g, 14.7 mmol) was dissolved in acetonitrile (200 mL), and iodopropane (1.72 mL, 17.7 mmol) and K$_2$CO$_3$ (5.0 g, 36.9 mmol) were added. The reaction mixture was allowed to reflux for 15 h. after the mixture was cooled to ambient temperature, aqueous Na$_2$CO$_3$ (10%, 100 mL) was added, and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 × 50 mL) and the combined organic phase was washed with brine, dried (MgSO$_4$), and concentrated in vacuo to give 4.2 g of crude product. Purification with flash chromatography using CH$_2$Cl$_2$/MeOH [1:1 (v/v)] as eluent afforded pure **12b** (3.28 g, 79%). MS *m/z* (relative intensity, 70 eV) 281

(M$^+$, 5), 252 (bp), 129 (20), 115 (20), 70 (25). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ ppm 0.96 (t, $J$ = 7.3 Hz, 3 H), 1.53−1.64 (m, 2 H), 1.89 (dd, $J$ = 9.6, 3.54 Hz, 4 H), 2.03−2.14 (m, 2 H), 2.31−2.41 (m, 2 H), 2.64 (ddd, $J$ = 15.4, 5.7, 5.5 Hz, 1 H), 3.06−3.15 (m, 5 H), 7.51−7.58 (m, 2 H), 7.78−7.86 (m, 2 H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ ppm 11.98, 20.18, 33.29, 42.59, 44.43, 54.06, 60.93, 124.99, 125.74, 129.39, 132.04, 148.28. The amine was converted to the HCl salt and recrystallized in EtOH/diethyl ether: mp 212−214 °C. Anal. (C$_{15}$H$_{24}$ClNO$_2$S) C, H, N.

**Note Added after ASAP Publication.** This paper was published ASAP on February 15, 2010 with errors in Figures 5 and 6. The revised version was published on February 23, 2010.

**Supporting Information Available:** Experimental details of the synthesis of **9a**−**12a**; biological methods and methods of preparing LClogD values. This material is available free of charge via the Internet at http://pubs.acs.org.

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