Towards a New Generation of Potential Antipsychotic Agents Combining D_2 and 5-HT_{1A} Receptor Activities

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We report the discovery and the synthesis of novel, potential antipsychotic compounds combining potent dopamine D_2 receptor antagonist and serotonin 5-HT_{1A} receptor agonist properties in the same molecule. We describe the structure−activity relationship that lead us to the promising derivative: *N*-[(2,2-dimethyl-2,3-dihydro-benzofuran-7-yloxy)ethyl]-3-(cyclopent-1-enyl)-benzylamine **16**. The latter has high affinity for D_2 and 5-HT_{1A} receptors, whereas it possesses only a weak affinity for 5-HT_{2A} sites. In cellular models of signal transduction, **16** behaves as a silent antagonist at rD_2 receptors while activating h5-HT_{1A} receptors with an efficacy at least equivalent to that of the prototypical 5-HT_{1A} agonist (±)-8-OH-DPAT. These dual actions confer a unique pharmacological profile to the product. In a behavioral model predictive of positive symptoms, **16** has an activity comparable to that of the typical antipsychotic haloperidol, while it is devoid of cataleptogenic effects. Although it produces behaviors characteristic of 5-HT_{1A} receptor activation in rats, these occur at doses 100 times higher than those with (±)-8-OH-DPAT. We believe that the relative balance of D_2 and 5-HT_{1A} actions in **16** is appropriate, possibly optimal, to ensure superior efficacy and tolerability over existing antipychotic drugs.

Introduction

Schizophrenia is a lifelong, complex psychotic disorder. The characteristic symptoms of the disease have been classified into positive, negative, and cognitive. Depression is also a common feature of the condition.[1] In many patients the illness involves repeated relapses of acute psychotic episodes interspersed with stable phases of complete or partial remission. The introduction of antipsychotics in the late 1950s was a major advance in the management of schizophrenia and all effective antipsychotic drugs identified to date block D_2 receptors.[2] However, although blockade of D_2 receptors improves the positive symptoms, it also accounts for side effects that undermine compliance, in particular extrapyramidal effects[3] (EPS) and hyperprolactinemia.[4] It took nearly three decades to obtain drugs that cause no or minimal EPS at therapeutically relevant doses. These second-generation derivatives, categorized as atypical in contrast to conventional D_2 blockers, combined D_2 and 5-HT_2 antagonism (e.g., clozapine, risperidone, olanzapine, and ziprazidone).[5] They are claimed to be active against both positive and negative symptoms, even though their superiority on negative symptoms compared with that of typical antipsychotics is by no means firmly established.[6] Except for clozapine in treatment-resistant schizophrenia, comparative studies have not shown efficacy advantage for any one of these agents, and treatment discontinuation rates are very high.[7] Newer atypical agents (i.e., aripiprazole, bifeprunox, SSR-181507) differ in that they act as partial agonists at D_2 receptors, although they also interact with an array of other CNS targets. Such therapeutic strategy features the stabilization of dopamine function, instead of the inhibition of D_2 transmission caused by previous antipsychotic drugs.[8] Consequently, the capacity of drugs such as aripiprazole to reduce positive symptoms has been questioned, and they may still be associated with adverse effects originating from D_2 blockade.[9] The search for more effective and less toxic therapies for schizophrenia, therefore, continues. Another pharmacological approach, which has been gaining ground steadily, involves combining D_2 antagonism and 5-HT_{1A} agonism in the same molecule.[10] Indeed, numerous mechanistic considerations[11] and preclinical evidence[12] support the potential of such a combination. At present, however, compounds having varying ratios of D_2 and 5-HT_{1A} activities for an adequate pharmacological and clinical evaluation are lacking.

The work described herein falls within this framework. Thus, we examined the relationship between D_2 and 5-HT_{1A} activities in novel hybrid D_2 antagonists and 5-HT_{1A} agonists, and then we evaluated the impact of some of these derivatives in behavioral models.

The optimal D_2 and 5-HT_{1A} pattern cannot be predicted today; therefore, our research effort was guided by two basic considerations: (1) A first-line antipsychotic treatment should control the positive symptoms. From a mechanistic point of view, this translates into compounds endowed with potent antagonist properties at D_2 receptors. (2) The extent of 5-HT_{1A} stimulation to be introduced into a dual D_2/5-HT_{1A} agent must be sufficient to prevent catalepsy in rodents, even at high doses; taking into account that the blockade (or perhaps the negative activation) of D_2 receptors evokes catalepsy in rodents and EPS in human.[13]

Previous studies from this laboratory[14a] have already established that the catalepsy produced by a fixed dose of haloperidol[14b] could be reversed, in a dose-related manner, by the coadministration of 5-HT_{1A} agonists; however, effective reversal required an intrinsic activity at least equivalent to that of (±)-8-OH-DPAT.[14c] Though the context is slightly different here, because we deal with a single agent acting at both D_2 and 5-HT_{1A} receptors, this precedent has the merit to define a rational threshold for 5-HT_{1A} activation. The profile we aimed at is as follows: (1) potent D_2 antagonist properties and (2) a 5-HT_{1A} efficacy at least equivalent to that of (±)-8-OH-DPAT.[15]

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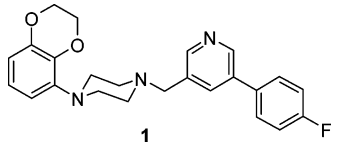
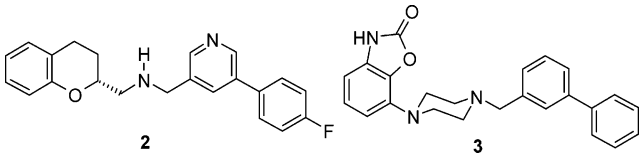


1

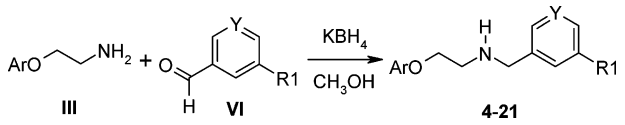
Figure 1. Structure of SLV313.



2 **3**

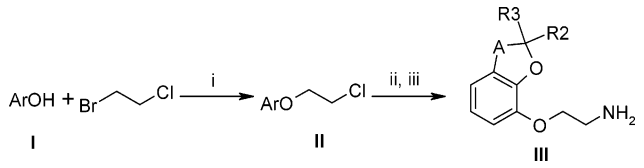
Figure 2. Structure of sarizotan (left); structure of bifeprunox (right).

Scheme 1. General Method for the Synthesis of Compounds **4**−**21**



III **VI** **4-21**

Scheme 2. Preparation of Amines **III**



I **II** **III**

Reagents and conditions: (i) 1-bromo-2-chloroethane, K_2CO_3, ethylmethylketone, 80 °C; (ii) potassium phtalimide, DMF, 150 °C; (iii) ethanolamine, 25 °C.

Among the known and putative antipsychotics, the profile of **1** (SLV313) comes closest to that which we were interested in (Figure 1).[16] This prompted us to modify the structure of **1** to obtain novel derivatives that met our pharmacological requirements. At first we explored alternatives to the biaryl subunit in **1**, then we optimized the component that conveys the 5-HT_{1A} activity. In the last part of this work, we report and discuss in vivo results on the most promising derivatives in comparison with reference compounds.

Chemistry

The general synthetic route used for the preparation of compounds **4**−**21** is described in Scheme 1. Thus, a reductive amination between amines **III** and aldehydes **VI** provided a convergent strategy to access the target compounds **4**−**21**.

The amines **III** were either known[17,18] or prepared in a straightforward fashion (Scheme 2). Thus, a Williamson reaction with 1,2-bromochloroethane added the two-carbon chain on either a preformed or commercially available substituted phenol or benzofuranol ring.[19] From intermediate **II**, a classic, two-step Gabriel synthesis[20] served to introduce the primary amine function present in compounds **III**.

The preparation of the aldehydes **VI** is depicted in Schemes 3 and 4. In any case, the synthesis started from a disubstituted phenyl (or pyridyl) ring containing an ester or an aldehyde function and a halogen atom in the *meta*-position.

From the commercially available 3-haloethylbenzoate (Scheme 3), a Heck coupling reaction[21] with the cycloalkene of appropriate ring-size delivered the unconjugated aryl-cycloalkene (Method A). The double bond of the latter was then either isomerized into the thermodynamic, conjugated position using rhodium(III) chloride[22] to provide **IVe**−**g** or hydrogenated to give **IVh**. The known aldehyde **VIi**[23] was obtained according to Method B. A Stille coupling reaction[24] between 3-iodoethylbenzoate and tributylvinyltin led to the corresponding styrene, which was then converted to the cyclopropane **IVi** by a Simmons−Smith reaction.[25] The oxidation level of the intermediates **IVe**−**i** was subsequently adjusted by reduction to the primary alcohols ($LiAlH_4$) then reoxidation with MnO_2. Overall, this two-step sequence delivered compounds **VI** with good efficiency.

The aromatic substituents of interest (i.e., R_1 = Ph, thienyl, or furyl) were incorporated by a palladium-catalyzed reaction (Method C). For this purpose, 3-bromobenzaldehyde was subjected to a Suzuki cross-coupling[26] reaction with the appropriate boronic acids to yield the known aldehydes **VIa**−**d** in a single step.[17,27−30]

Finally, the pyridine analogue of **VIg** (i.e., **VIj**) was prepared as outlined in Scheme 4.[31] Addition of the Grignard reagent derived from 1,4-dibromobutane[32] on 3-bromo-5-ethylnicotinate followed by dehydration of the resulting tertiary alcohol gave the derivative **V**. The aldehyde function was then installed via bromine−lithium exchange and trapping of the aryllithium with *N*-formylmorpholine. This procedure supplied the derivative **VIj** in modest yield.[33]

Results and Discussion

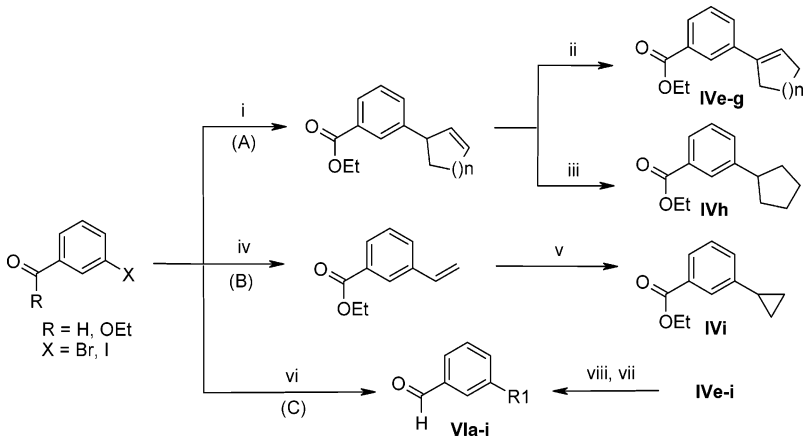
The biarylmethylamino motif, such as that found in **1**, is shared by the antidyskinetic agent **2** (sarizotan),[34] the antipsychotic **3** (bifeprunox),[35] and a few other ligands[36] interacting with different members of the D_2 receptors family; highlighting the versatility of this chain (Figure 2).

Our efforts to find a group different from the biarylmethylamino fragment in **1** that mimicked its action was totally unrewarding as long as chemical modulations were exercised on an arylpiperazine template. Because replacement of either of the aromatic rings of the biaryl subunit was incompatible with maintaining a useful level of interactions at 5-HT_{1A} and/or D_2 receptors,[37] we abandoned this strategy. The presence of a chroman in **2** suggested another possibility. Disconnection between C2−C3 in the dihydro-pyran part of **2** reveals an *ortho*-substituted aryloxyethylamino moiety. It turned out that such a change in connectivity produced more flexible ligands that then withstood broad variations in the nature of R_1 (see Table 1).[38a] From our previous experience[38b] and literature precedent,[38c] we selected a 2-isopropyloxyethylamino as a platform for launching a SAR at the biaryl moiety.

First, simplifying the 4-fluorophenyl-pyridinyl to a naked biphenyl, such as that carried by **3**, led to **4**. As shown in Table 1, the affinity balance in **4** was shifted in favor of the D_2 component at the expense of 5-HT_{1A} (**4** vs **1**). This reversal in the order of affinities ($pK_i[D_2] > pK_i[5\text{-}HT_{1A}]$), as compared to **1**, fitted our plans (vide supra). Moreover, **3** is developed as an antipsychotic ($D_2 > 5\text{-}HT_{1A}$), whereas **2** ($5\text{-}HT_{1A} > D_2$) was in clinical trials for reducing levodopa-induced dyskinesia in patients suffering from Parkinson's disease. Compound **4** maintained a substantial affinity for 5-HT_{1A} receptors while that for 5-HT_{2A} receptors was weak. In the recombinant system used, **4** appeared to be a less potent agonist at h5-HT_{1A} receptors than **1**, although the amplitude of the maximal response it attained was encouragingly high.

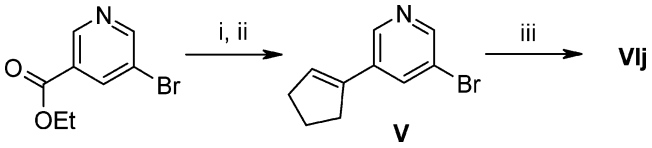
Introduction of 5-membered ring phenyl bioisosteres at the terminal position has little influence on D_2 and 5-HT_{1A} affinities (**5**, **6**, and **7** vs **4**). The results from GTPγS signaling, on the other hand, revealed clear differences between these products. Thus, **5** and **7** lacked 5-HT_{1A} agonist activity, whereas **6** behaved as a partial agonist of moderate potency, reaching nearly half of the response to 5-HT, suggesting a possible, positive contribution of the S-3 atom in the thiophene. Such isosteric

Scheme 3. Preparation of Aldehydes **VIa−i**



Reagents and conditions: Method A, (i) $Pd(OAc)_2$, PAr_3, K_2CO_3, cycloalkene, DMF; (ii) $RhCl_3$, EtOH, Δ; (iii) H_2, Pd/C, EtOH; Method B, (iv) $Pd(PPh_3)_4$, CuI, tributylvinyltin, 1,4-dioxane; (v) CH_2ClI, Et_2Zn; Method C, (vi) $Pd(PPh_3)_4$, Na_2CO_3, boronic acid, DME; (vii) $LiAlH_4$, THF; (viii) MnO_2, $CHCl_3$.

Scheme 4. Preparation of Aldehyde **VIj**



Reagents and conditions: (i) $Br(CH_2)_4Br$, Mg, THF; (ii) HCl, $PhCH_3$, Δ; (iii) *n*-BuLi, *N*-formylmorpholine, Et_2O.

replacement, when attempted at the internal phenyl, ended up in a dramatic loss of affinity at D_2 and 5-HT_{1A} sites (data not shown).

The finding that partial (**8**−**10**) or complete reduction (**11** and **12**) of the terminal aromatic nucleus gave derivatives that still interacted with D_2 and 5-HT_{1A} receptors represented a major step forward in the project. Within the cycloalkene subset (i.e., **8**−**10**), binding affinity at D_2 receptors was inversely related to the ring size of the substituent R_1. No such trend was observed at 5-HT_{1A} receptors, and the affinities for compounds **8**−**10** remained of similar magnitude. All these ligands (**8**−**11**) exerted partial agonist effects in HeLa cells. However, the gap separating affinity (measured through [^{3}H]8-OH-DPAT displacement) from potency (measured through G-protein activation) was significantly smaller with **10** than with the other derivatives. Assuming that this difference ($pK_i - pEC_{50}$) somehow reflects a higher degree of sensitivity of the functional assay toward ligands containing a phenyl-3-cyclopenten-1-yl fragment (e.g., **10**), we settled on such a motif to optimize the remainder of the molecule. In addition, the benzylamino-cyclopentenyl was a novel chemo-type and, therefore, well-suited for chemical modifications.

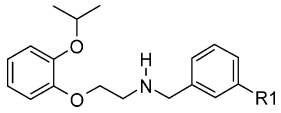
As a logical extension, we next refined the aryloxyethylamino component, using **10** as a model. Again, the modulations we incorporated were inspired by the structure of **1**. Thus, the isopropylether and the 1,4-dioxan functions in **10** and **1**, respectively, were amalgamated to give rise to the novel series reported in Table 2. Accordingly, formation of a six-membered di-oxygenated ring (e.g., **13**) did not affect the binding at D_2 sites (**13** vs **10**) but markedly enhanced affinity and functional activity at 5-HT_{1A} receptors. In contrast, reducing the size of the fused ring (**14** vs **13**) turned out to be detrimental on both D_2 and 5-HT_{1A} parameters. This trend could be reversed by raising the lipophilicity of the molecule through removal of the O-3 atom in the methylenedioxy (e.g., **16**) and introduction of a *gem*-dimethyl group next to the oxygen (e.g., **15**). Thanks to these modifications, high affinity at D_2 receptors could be achieved (**16**−**19**) with the exception of compound **18**. The comparison between **18** and **16** indicated that binding at D_2 receptors was sensitive to steric hindrance in the region of R_2 and R_3 on the dihydrobenzofuran ring (DHF).

So, clearly, the substituent(s) positioned on the DHF influenced affinity data. A *gem*-dimethyl group in position 2 on the DHF improved both D_2 and 5-HT_{1A} affinities (**14** vs **15**), although the D_2 binding site does not tolerate larger groups than a methyl at this position (vide supra). A *gem*-dimethyl group in position 3 on the DHF markedly decreased the affinity for 5-HT_{1A} subtype (**19** vs **16**), whereas that for D_2 was preserved.[39]

Derivatives **15**−**17** were, at least, as potent as 8-OH-DPAT at activating the h5-HT_{1A} receptors (*cf.* Table 2). Not unexpectedly from the structure of **1**, the pyridin-3-yl analogues **20** and **21** of **16** and **17** exhibited higher D_2 and 5-HT_{1A} affinities and were also more potent in the GTPγS assay. Most of the compounds **13**−**21** behaved as antagonists at D_2 receptors.[40,41] Overall, compounds **16** and **20** fulfilled the pharmacological requirements defined at the outset: they bind with high affinities to and are antagonists at D_2 receptors while they act as potent 5-HT_{1A} agonists. Consequently, both were investigated in vivo. Given that, in this study, the value of the intrinsic activity of (±)-8-OH-DPAT set the target to eliminate catalepsy, it is included as a reference in Table 2.

The indirect dopamine receptor agonist methylphenidate reliably produces stereotypy and hyperlocomotion in rats. The reversal of the signs (i.e., gnawing, sniffing, rearing, and locomotion) mediated by a high dose of methylphenidate (40 mg/kg, i.p.) was, therefore, taken as a measure of antidopaminergic effects in vivo. Further, because methylphenidate induces psychotic-like symptoms in humans (e.g., delirium and hallucinations), it was assumed that normalization (i.e., inhibition of all the signs) of such a high dose of methylphenidate-induced responses in rats is predictive of an "incisive" activity against positive symptoms in schizophrenics.[42] Consistent with this, the D_2 antagonist and typical antipsychotic haloperidol completely counteracts all the behaviors of methylphenidate-treated rats with an ED_{50} value of 0.31 mg/kg (cf. Table 3). Similarly, normalization occurred with **16** and **20**, and both compounds were more effective than **1**. Hence, these results confirmed the ability of **16** and **20** to inhibit dopamine hyperactivity in vivo. In addition, the activity of **16** and **20** in the methylphenidate test demonstrated that their 5-HT_{1A} agonist properties do not mask their D_2 antagonist action. Extrapolating from this animal data, we

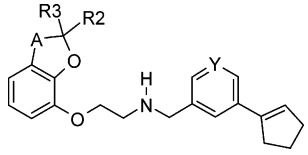
Table 1. In Vitro Activities of Compounds **1**−**12**



		affinity, pK_i[a]			5-HT_{1A} efficacy	
cmpd	R_1	D_2	5-HT_{2A}	5-HT_{1A}	pEC_{50}[b]	E_{max}[c]
1		8.40 ± 0.05	6.14 ± 0.02	8.64 ± 0.01	8.23 ± 0.06	45.3 ± 3.5
2		7.72 ± 0.05	5.67 ± 0.07	8.65 ± 0.02	7.11 ± 0.05	66.5 ± 1.9
3		8.81 ± 0.04	5.48 ± 0.06	7.19 ± 0.14	6.49 ± 0.20	60.8 ± 1.8
4	phenyl	9.71 ± 0.12	6.14 ± 0.02	7.58 ± 0.06	5.85 ± 0.15	73.9 ± 2.5
5	thien-2-yl	9.25 ± 0.16	6.25 ± 0.02	7.33 ± 0.03	<5	
6	thien-3-yl	9.56 ± 0.07	6.46 ± 0.05	7.46 ± 0.06	7.17 ± 0.01	47.7 ± 8.5
7	fur-2-yl	9.47 ± 0.15	6.43 ± 0.08	7.17 ± 0.07	<5	
8	cyclohepten-1-yl	8.51 ± 0.11	5.98 ± 0.11	7.64 ± 0.30	5.81 ± 0.07	86.5 ± 2.5
9	cyclohexen-1-yl	8.81 ± 0.10	6.72 ± 0.10	7.91 ± 0.10	7.33 ± 0.05	69.8 ± 3.7
10	cyclopenten-1-yl	9.30 ± 0.06	6.19 ± 0.09	7.53 ± 0.10	7.16 ± 0.07	54.0 ± 5.8
11	cyclopentanyl	9.25 ± 0.07	6.52 ± 0.03	7.78 ± 0.09	6.71 ± 0.23	71.2 ± 3.5
12	cyclopropyl	9.22 ± 0.07	6.96 ± 0.02	7.21 ± 0.03	<5	
Haloperidol		8.36 ± 0.05	7.08 ± 0.03	5.77 ± 0.04		

[a] Binding affinity values are expressed as means ± SEM of separate experiments, each performed in triplicate. [b] Concentration of agonist for a 50% of [^{35}S]GTPγS binding in HeLa cells expressing human 5-HT_{1A} receptors, −Log EC_{50} (pEC_{50}) values were estimated using the mean values of three separate experiments. [c] E_{max} refers to maximal agonist effect, results expressed as % relative to serotonin (100%).

Table 2. In Vitro Activities of Compounds **13**−**21**



					affinity, pK_i[a]		5-HT_{1A} efficacy	
cmpd	A	R_2	R_3	Y	D_2	5-HT_{1A}	pEC_{50}[b]	E_{max}[c]
13	OCH_2	H	H	CH	9.11 ± 0.08	8.77 ± 0.01	8.19 ± 7.30	68.9 ± 4.7
14	O	H	H	CH	8.59 ± 0.04	7.68 ± 0.07	6.87 ± 0.02	70.7 ± 1.3
15	O	CH_3	CH_3	CH	8.91 ± 0.06	8.02 ± 0.03	7.61 ± 0.04	90.6 ± 12.2
16	C	CH_3	CH_3	CH	9.38 ± 0.05	8.24 ± 0.07	8.00 ± 0.04	85.6 ± 4.4
17	C	CH_2	CH_2	CH	8.95 ± 0.24	8.21 ± 0.14	7.47 ± 0.11	93.8 ± 5.5
18[d]	C	CH_3	CH_2CH_3	CH	7.94 ± 0.17	8.26 ± 0.01	7.49 ± 0.09	77.7 ± 1.7
19	$C(CH_3)_2$	H	H	CH	9.09 ± 0.07	7.37 ± 0.14	6.95 ± 0.09	72.4 ± 5.5
20	C	CH_3	CH_3	N	9.56 ± 0.07	9.02 ± 0.10	8.54 ± 0.04	72.4 ± 1.5
21	C	CH_2	CH_2	N	9.35 ± 0.10	8.44 ± 0.12	8.58 ± 0.01	78.5 ± 1.0
8-OH-DPAT					6.26 ± 0.03	8.85 ± 0.07	7.55 ± 0.11	82.0 ± 4.0

[a] Binding affinity values are expressed as means ± SEM of separate experiments, each performed in triplicate. [b] Concentration of agonist for a 50% of [^{35}S]GTPγS binding in HeLa cells expressing human 5-HT_{1A} receptors, −Log EC_{50} (pEC_{50}) values were estimated using the mean values of three separate experiments. [c] E_{max} refers to maximal agonist effect, results expressed as % relative to serotonin (100%). [d] Racemate.

Table 3. Activities of Compounds **16** and **20** and References in Rats

cmpd	LLR[a] ED_{50}[b]	FBP[c] ED_{50}	normalization[d] ED_{50}	LLR/N[e]	CLP[f] ED_{50}	CLP/N[e]
1	0.32 (0.07−1.4)	1.70 (0.63−4.5)	1.4 (0.63−3.10)	0.2	>40	>28
Haloperidol			0.31 (0.17−0.57)		0.30 (0.16−0.55)	1
8-OH-DPAT	0.09 (0.05−0.17)	0.28 (0.17−0.47)	>10		>10	
16	8.3 (2.6−26)	32 (10−102)	1.10 (0.70−1.80)	7.5	>40	>36
20	1.8 (0.69−4.8)	4.7 (0.88−25)	0.29 (0.13−0.64)	6.2	>40	>137

[a] LLR induction scored at 15 min after treatment i.p. [b] ED_{50} effective dose values are mg/kg (95% confidence limit). [c] FBP at 15 min after treatment i.p.; compounds **16** and **20** did not produced any FPT at 40 mg/kg i.p. [d] Potency of the compound at normalizing methylphenidate-induced behaviors (gnawing, sniffing, rearing, and locomotion), scored 30 min after the injection i.p. [e] N stands for normalization. [f] Potency of the compound at inducing catalepsy in rats measured by the crossed-leg position test, scored at 60 min after injection.

anticipated that **16** and **20** would relieve the psychotic symptoms in humans in a range of doses comparable as that of haloperidol.

To complement the profile associated with the blockade of D_2 receptors, the cataleptogenic potential of compounds **16** and **20** (along with that of references) was evaluated in rats.[43] As discussed in the introduction, the absence of cataleptogenic effects is considered as an absolute requirement for any new antipsychotic. As shown in Table 3, haloperidol evoked catalepsy at the same doses as those that normalized methylphenidate-induced behaviors (i.e., from 0.30 mg/kg onward); this result fully agrees with the high capacity of this drug to block D_2 subtypes in striatal structures.[44] In contrast, no cataleptogenic activity was observed with compounds **16** and **20** at doses up to 40 mg/kg, despite their definite D_2 antagonist properties in vivo (vide supra). Additional studies showed that catalepsy was restored when **16**-treated animals were pretreated with the selective 5-HT_{1A} antagonist WAY-100635 (1 mg/kg, i.p.); this is direct evidence that the anticataleptogenic properties of **16**

Table 4. Experimental Details for Each of the Binding Assays[a]

binding site	[^{3}H]ligand (nM)	K_d (nM)	tissue (mg/mL)	incubation time (min)	incubation buffer	nonspecific binding (μM)
5-HT_{1A}	8-OH-DPAT (0.2)	3.1	rat cortex (10)	30	B	5-HT (10)
5-HT_{2A}	ketanserin (0.2)	3.1	rat cortex (10)	30	B	methysergide (10)
D_2	YM-09151-2 (0.05)	0.036	rat striatum (1)	60	A	(+)-butaclamol (1)

[a] Incubation temperature 23 °C. Buffer A: Tris-HCl 50 mM, pH 7.4; NaCl 120 mM; KCl 5 mM. Buffer B: Tris-HCl 50 mM, pH 7.4; pargyline 10 μM; $CaCl_2$ 4 mM; ascorbic acid 0.1%.

are mediated by its 5-HT_{1A} agonist action.[45] Importantly, catalepsy did not appear upon repeated administration of **16**, indicating that no tachyphilaxis to the 5-HT_{1A} anticataleptogenic effects developed over (sub)chronic treatment (data not shown).

If the ratio CLP/normalization gave an indication about the therapeutic margin for antipsychotic-like versus EPS-like effects, then a favorable index was achieved with compounds **16** and **20** (Table 3). In essence, compounds **16** and **20** may be as effective as the typical antipsychotics on the positive symptoms while resembling the atypical ones with respect to EPS.[46]

In the present study, we used lower lip retraction (LLR) as a sensitive marker of central 5-HT_{1A} activation.[47] Flat body posture[48] (FBP) was also recorded as it represents one component of the "5-HT syndrome" in rats.[49] After i.p. administration, all the compounds, except haloperidol, produced dose-related LLR and FBP (Table 3). In the case of **16**, LLR was not observed up to 8.3 mg/kg; a dose that is 25 and 100-fold higher than that of **1** and 8-OH-DPAT, respectively. Regarding FBP, the rank-order of the compounds in Table 3 was the same as for LLR, but the dose−response curves were shifted rightwards. The mechanism accounting for the low incidence of LLR (and FBP) observed with **16** is likely related to the dual activity at both D_2 and 5-HT_{1A} receptors. In any case, D_2 blockade seems to reduce the behavioral signs attributable to 5-HT_{1A} activation. Practically, there is a range of doses (i.e., 1.1 to 8.3 mg/kg) in which one can benefit from 5-HT_{1A} stimulation yet being free from any 5-HT behavioral manifestation. The span of doses separating the antipsychotic-like effects from the only element of the "5-HT syndrome" present (i.e., FBP) is even more impressive (i.e., 1.1 vs 32 mg/kg). However, the overlap between LLR in rat and any mild clinical symptoms in human, as well as the link between FBP and serotoninergic side effects, is a matter of great uncertainty.

Finally, if the ratio LLR/normalization gave an estimate of the (optimal) balance between D_2 and 5-HT_{1A} properties, then on this index, also, compound **16** stood out. In contrast, **20** may display too much 5-HT_{1A} activity relative to D_2.

Conclusions

In this paper, we report the process through which we discovered a series of structurally novel, potential antipsychotic agents. Among the compounds prepared, **16** and **20** exhibited high binding affinity for D_2 and 5-HT_{1A} receptors and only a weak affinity for 5-HT_{2A} receptors. They acted as antagonists at D_2 and as potent agonists at 5-HT_{1A} sites. Compounds **16** and **20** differ from **1** by their binding profiles (D_2 > 5-HT_{1A}) and higher functional activity at h5-HT_{1A} receptors. Conceptually, the compounds described in this work differ from the second-generation antipsychotics, regardless of whether those possess a 5-HT_{1A} component (e.g., aripiprazole, ziprazidone, and clozapine) or not (e.g., risperidone, olanzapine, and sertindole) by their lack of interaction at 5-HT_{2A} receptors.

In preclinical models, compounds **16** and **20** proved as effective as the typical antipsychotic haloperidol and were devoid of cataleptogenic effects. This absence of catalepsy resulted from 5-HT_{1A} receptors stimulation. In addition, the doses of **16** and **20** that produced 5-HT_{1A} signs in rats far exceed those of the prototypical agonist (±)-8-OH-DPAT and are not commensurate with their high efficacy in vitro.[50]

Several lines of evidence indicate that compounds **16** and close relatives may combine the advantages of typical and atypical antipsychotics. Further pharmacological characterization of **16**, and a few other members of the series, focusing on aspects that limit the therapeutic utility of available drugs (i.e., negative symptoms and cognitive deficits), are being published.[51] The data collected on these various aspects support the view that **16** may represent the prototype of a novel class of more "complete" antipsychotic agents.

Experimental Section

Chemistry. Melting points were determined on a Büchi 530 melting point apparatus and were not corrected. ^{1}H NMR spectra were recorded on a Bruker Avance 400 spectrometer operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C. Chemical shifts are reported in δ value (ppm) relative to an internal standard of tetramethylsilane. Infrared (IR) spectra were obtained on a Nicolet FT 510 P spectra photometer. Microanalyses were obtained on a Fison EA 1108/CHN analyzer. Mass spectra (TSQ 7000 Finnigan, Thermoelectron Corporation) were determined by electron spay ionization (ESI) or atmospheric pressure chemical ionization (APCI) techniques. Analytical thin-layer chromatography were carried out on precoated plates (silicagel, 60 F 254 Merck).

General Procedure for the Preparation of III. The following three-step preparation was used to synthesize all the amines **III** described in this paper.

2-Chloroethoxyaryl Ether (II). Potassium carbonate (1.6 equiv) and 1-bromo-2-chloroethane (3.5−4 equiv) were added to a solution of the corresponding phenol or benzofuranol derivative **I** (1 equiv) in ethylmethylketone (0.2−0.5 M). The reaction mixture was heated with stirring at 80 °C for 22 h then cooled to room temperature and concentrated in vacuo. Water was added and the product was extracted with methylene chloride. The combined organic layer was washed with sodium hydroxide (1 M), then with water and brine, dried over magnesium sulfate, and concentrated in vacuo. The ether **II** was not purified unless otherwise noted.

2-Aminoethoxyaryl Ether (III). Potassium phtalimide (1.05 equiv) was added by portion to a solution of **II** (1 equiv) in DMF (0.6 M), and the reaction mixture was plunged in a preheated oil bath at 150 °C. The mixture was stirred for 2 h then cooled to room temperature, poured into water, and extracted with methylene chloride. The combined organic layer was washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The solid obtained was recrystallized before cleavage of the phtalimido group. The phtalimido derivative (1 equiv) was dissolved in ethanolamine (0.3 M), and the solution was stirred at room temperature for 18 h. The reaction mixture was poured into cold water, and the product was extracted with methylene chloride. The combined organic layer was washed with brine, dried over sodium sulfate, and concentrated in vacuo. The amine **III** was used without purification, unless otherwise noted.

2-(Benzo[1,3]dioxol-4-yloxy)-ethylamine (IIIc). Synthesized according to the general procedure above from 2-[2-benzo[1,3]-

dioxol-4-yloxy)-ethyl]-isoindole-1,3-dione (6.50 g, 21 mmol) and ethanolamine (42 mL), compound **IIIc** was obtained as a yellow oil (3.30 g, 87%): ^{1}H NMR ($CDCl_3$) δ 3.1 (t, J = 5.2 Hz, 2H), 4.11 (t, J = 5.2 Hz, 2H), 5.95 (s, 2H), 6.52 (d, J = 8.1 Hz, 1H), 6.55 (d, J = 8.1 Hz, 1H), 6.76 (dd, J = 8.2, 8.1 Hz, 1H).

2-(2,2-Dimethyl-benzo[1,3]dioxol-4-yloxy)-ethylamine (IIId). From 2-[2-(2,2-dimethyl-benzo[1,3]dioxol-4-yloxy)-ethyl]-isoindole-1,3-dione (1.30 g, 3.83 mmol) and ethanolamine (8 mL), the product was purified by flash column chromatography (silica gel, methylene chloride/methanol/ammonia, 95:4.5:0.5) to give **IIId** as pale yellow oil (0.65 g, 80%): ^{1}H NMR ($CDCl_3$) δ 1.69 (s, 3H), 1.70 (s, 3H), 3.08 (t, J = 5.2 Hz, 2H), 4.10 (t, J = 5.2 Hz, 2H), 6.42 (d, J = 8.1 Hz, 1H), 6.54 (d, J = 8.5 Hz, 1H), 6.69 (dd, J = 8.3, 8.1 Hz, 1H).

2-(2,2-Dimethyl-2,3-dihydro-benzofuran-7-yloxy)-ethylamine (IIIe). From 2-[2-(2,2-dimethyl-2,3-dihydro-benzofuran-7-yloxy)-ethyl]-isoindole-1,3-dione (18 g, 0.056 mol) and ethanolamine (180 mL), compound **IIIe** was obtained as a pale yellow solid (10.20 g, 88%): mp = 56 °C; ^{1}H NMR ($CDCl_3$) δ 1.50 (s, 6H), 3.02 (s, 2H), 3.06 (t, J = 5.6 Hz, 2H), 4.07 (t, J = 5.6 Hz, 2H), 6.75 (m, 3H).

2-(2-Spirocyclopropane −2,3-dihydro-benzofuran-7-yloxy)-ethylamine (IIIf). From 2-[2-spirocyclopropane-2,3-dihydro-benzofuran-7-yloxy)-ethyl]-isoindole-1,3-dione (3 g, 8.94 mmol) and ethanolamine (15 mL), the product was purified by flash column chromatography (silica gel, methylene chloride/methanol/ammonia, 98:1.5:0.5) to give **IIIf** as a yellow oil (0.55 g, 30%): ^{1}H NMR ($CDCl_3$) δ 0.69 (t, J = 6.4 Hz, 2H), 1.28 (t, J = 6.4 Hz, 2H), 1.49 (s, 2H), 3.06 (t, J = 5.6 Hz, 2H), 3.32 (s, 2H), 4.07 (t, J = 5.6 Hz, 2H), 6.80−6.84 (m, 3H).

2-(2-Ethyl-2-methyl-2,3-dihydro-benzofuran-7-yloxy)-ethylamine (IIIg). From 2-[2-(2-ethyl-2-methyl-2,3-dihydro-benzofuran-7-yloxy)-ethyl]-isoindole-1,3-dione (0.72 g, 2.05 mmol) and ethanolamine (4 mL), compound **IIIg** was obtained as a yellow oil (0.32 g, 70%), which was used as such in the next step: ^{1}H NMR ($CDCl_3$) δ 0.95 (t, J = 7.6 Hz, 3H), 1.44 (s, 3H), 1.61 (br s, 2H), 1.78 (q, J = 7.6 Hz, 2H), 2.85 (t, J = 5.6 Hz, 2H), 3.58 (t, J = 5.6 Hz, 2H), 6.73−6.80 (m, 3H).

2-(3,3-Dimethyl-2,3-dihydro-benzofuran-7-yloxy)-ethylamine (IIIh). From 2-[2-(3,3-dimethyl-2,3-dihydro-benzofuran-7-yloxy)-ethyl]-isoindole-1,3-dione (2 g, 5.93 mmol) and ethanolamine (10 mL), the product was purified by flash column chromatography (silica gel, methylene chloride/ethanol/ammonia, 95:4.5:0.5) to afford **IIIh** as a yellow oil (1.05 g, 85%): ^{1}H NMR ($CDCl_3$) δ 1.34 (s, 6H), 1.66 (br s, 2H), 3.09 (t, J = 5.2 Hz, 2H), 4.07 (t, J = 5.2 Hz, 2H), 4.29 (s, 2H), 6.75−6.81 (m, 2H), 6.82−6.86 (m, 1H).

General Procedure for the Preparation of Aldehydes (VIe−i), Method A. Step i. To a solution of ethyl 3-iodobenzoate (1 equiv) in DMF (5 mL/g) was successively added the corresponding cycloalkene (5 equiv), tetrabutylammonium bromide (1 equiv), potassium carbonate (2.5 equiv), tris-(*o*-tolyl) phosphine (0.05 equiv), and palladium acetate (0.025 equiv). The reaction mixture was heated at 110 °C for 16 h then cooled to room temperature, poured into water, and extracted with ethyl acetate. The combined organic layer was washed with brine and dried over magnesium sulfate, and the solvent was removed in vacuo. Purification of the residue was effected either by distillation or flash column chromatography.

Step ii. The product from step i was dissolved in ethanol (3 mL/mmol) and rhodium(III) chloride was added (0.1 equiv). The reaction mixture was heated at 80 °C for 16 h then cooled to room temperature. The catalyst was filtered off (Celite), and the solvent was removed in vacuo. Purification of the product **IV** was effected either by distillation or flash column chromatography.

Step vii. The ester **IV** was dissolved in diethyl ether, and this solution was added dropwise to a suspension of $LiAlH_4$ (1.1 equiv) in diethyl ether maintained at 0 °C. The reaction mixture was slowly warmed to room temperature and stirred until all the starting material was consumed (TLC). The reaction mixture was then cooled to 0 °C, and a 10% aqueous sodium hydroxide solution (5 mL per g of $LiAlH_4$) was added dropwise. After 10 min at 0 °C and 30 min at room temperature, the solid that formed was filtered off and washed with diethyl ether. The filtrate was concentrated in vacuo, and the residue obtained was used as such in the next step.

Step viii. The alcohol from step vii was dissolved in chloroform (20 mL/g) and manganese(IV) oxide was added in one portion (5 g per g of alcohol). The suspension was vigorously stirred for 16 h then filtered on a pad of silica, eluting with chloroform. The filtrate was concentrated in vacuo to give the aldehydes **VIe−i**, which were used as such in the next step or purified by flash column chromatography.

3-Cyclohepten-1-yl-benzaldehyde (VIe). From **IVe**, the aldehyde **VIe** was prepared in 88% yield (over 2 steps). It was purified by flash column chromatography (silica gel, cyclohexane/ethyl acetate, 90:10); yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.54−1.60 (m, 2H), 1.66−1.69 (m, 2H), 1.83−1.87 (m, 2H), 2.29−2.34 (m, 2H), 2.77−2.83 (m, 2H), 6.17 (t, J = 6.7 Hz, 1H), 7.45 (dd, J = 7.7, 7.6 Hz, 1H), 7.57 (dd, J = 6.5, 1.6 Hz, 1H), 7.59 (d, J = 9.2, 1 Hz, 1H), 7.82 (s, 1H), 10.01 (s, 1H).

3-Cyclohexen-1-yl-benzaldehyde (VIf). From **IVf**, the aldehyde **VIf** was prepared in 83% yield (over 2 steps). It was purified by flash column chromatography (silica gel, cyclohexane/ethyl acetate, 90:10); yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.59−1.71 (m, 2H), 1.78−1.82 (m, 2H), 2.22−2.25 (m, 2H), 2.41−2.44 (m, 2H), 6.21−6.23 (m, 1H), 7.46 (dd, J = 7.7, 7.6 Hz, 1H), 7.63 (dd, J = 7.7, 1 Hz, 1H), 7.73 (dd, J = 8.2, 1 Hz, 1H), 7.88 (d, J = 1 Hz, 1H), 10.02 (s, 1H).

3-Cyclopenten-1-yl-benzaldehyde (VIg). From **IVg**, the aldehyde **VIg** was prepared in 96% yield (over 2 steps). It was not purified at this stage; colorless oil: ^{1}H NMR ($CDCl_3$) δ 2.01−2.07 (m, 2H), 2.53−2.58 (m, 2H), 2,68−2.74 (m, 2H), 6.30 (br s, 1H), 7.49 (dd, J = 7.6, 7.5 Hz, 1H), 7.70−7.73 (m, 2H), 7.91 (s, 1H), 10.02 (s, 1H).

3-Cyclopentanyl-benzaldehyde (VIh). A solution of (3-ethylbenzoate)cyclopentene (0.80 g, 4.64 mmol) in ethyl acetate (24 mL) containing diisopropylethyl amine (3.20 mL, 18.6 mmol) and a catalytic amount of Pd(0) (5% on C) was stirred under hydrogen (balloon) for 4 h at room temperature. The suspension was filtered on Celite, and the filtrate was washed with HCl (1 N), water, and brine, dried over sodium sulfate, and filtered, and the solvent was evaporated in vacuo. The reduction−oxidation was followed as above, and the compound was isolated by flash column chromatography (silica gel, cyclohexane/ethyl acetate, 88:12) to give **VIh** (0.59 g, 70% over 2 steps) as a colorless oil: ^{1}H NMR (DMSO-d_6) δ 1.39−1.57 (m, 2H), 1.64−1.68 (m, 2H), 1.75−1.81 (m, 2H), 2.04−2.20 (m, 2H), 2.98−3.21 (m, 1H), 7.51 (dd, J = 7.67, 7.5 Hz, 1H), 7.60 (d, J = 7.6 Hz, 1H), 7.71 (d, J = 7.5 Hz, 1H), 7.79 (s, 1H), 10.03 (s, 1H).

5-Cyclopenten-1-yl-pyridine-3-carboxaldehyde (VIj). A solution of 3-bromo-5-cyclopenten-1-yl-pyridine (1 g, 4.46 mmol) in 25 mL of diethyl ether was added to a solution of *n*-butyl lithium (1.6 M in hexane, 4.20 mL, 6.68 mmol) in 25 mL of diethyl ether at −60 °C. The reaction mixture was stirred for 2 h at −60 °C, and then 4-morpholinecarboxaldehyde (1.40 mL, 13.38 mmol) was added. The reaction mixture was stirred for 1 h at −60 °C and then quenched with water, washed with brine, dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, cyclohexane/ethyl acetate, 80:20) to afford **VIj** (0.38 g, 49%) as an off-white solid, mp = 50 °C: ^{1}H NMR ($CDCl_3$) δ 2.09−2.11 (m, 2H), 2.60−2.62 (m, 2H), 2.70−2.73 (m, 2H), 6.49 (s, 1H), 8.32 (s, 1H), 8.89 (s, 1H), 8.93 (s, 1H), 10.10 (s, 1H).

General Procedure for the Formation of Products 4−21 from III and VI. A methanol solution (0.3 M) of the amine **III** (1 equiv) and aldehyde **VI** (1 equiv) was stirred at room temperature for 15 h. The reaction mixture was cooled to 0 °C, and potassium borohydride (2 equiv) was added by portions. The reaction was then allowed to warm to room temperature and stirred for 4 h. The mixture was concentrated to one-third of its volume, poured into water, and extracted with ethyl acetate, the combined organic layer was washed with brine, dried over sodium sulfate, and filtered, and

the solvent removed in vacuo. The residue was purified by flash column chromatography. The purified product (1 equiv) was then dissolved in ethanol and to this solution was added an ethanol solution of the appropriate acid (1 equiv). The mixture was concentrated to one-third its volume, and the salt that crystallized out was filtered, washed with ether, and dried. The purity of the salified material was systematically controlled by HPLC before pharmacological tests (HPLC: chrom type, fixed WL chromatogram, 220 nm; column type, symmetry C8 5μ 250 × 4.6 mm WAT; temperature, 25 °C; flow, 1 mL/min; peak quantification, area).

[2-(2-Isopropoxy-phenoxy)-ethyl]-(3-phenyl-benzyl)-amine (4). Reductive amination between **IIIa** (0.30 g, 1.53 mmol) and **VIa** (0.28 g, 1.53 mmol) and then purification by flash column chromatography (silica gel, methylene chloride/methanol/ammonia, 95:4.5:0.5) afforded 0.39 g (70%) of **4** as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.37 (d, J = 6 Hz, 6H), 3.18 (t, J = 5.1 Hz, 2H), 4.07 (s, 2H), 4.27 (t, J = 5.1 Hz, 2H), 4.55 (hept, J = 6 Hz, 1H), 6.98−7.06 (m, 5H), 7.32−7.44 (m, 6H), 7.66−7.77 (m, 3H). As the oxalate salt: white powder, mp = 182 °C; HPLC purity 99.7% (eluent, acetonitrile/water/KH_2PO_4, 450:550:6.8 g, pH 4); IR (KBr) ν 3432, 2973, 1752, 1500 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.22 (d, J = 6 Hz, 6H), 3.32 (t, J = 5.2 Hz, 2H), 4.27 (t, J = 5.2 Hz, 2H), 4.38 (s, 2H), 4.57 (hept, J = 6 Hz, 1H), 6.91 (dd, J = 7.5, 1 Hz, 1H), 6.95 (dd, J = 7.6, 1 Hz, 1H), 7.03 (dd, J = 7.9, 1.4 Hz, 2H), 7.4 (t, J = 7.3 Hz, 1H), 7.5 (t, J = 7.8 Hz, 2H), 7.51−7.66 (m, 2H), 7.68−7.72 (m, 3H), 7.87 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 21.8(2C), 45.2, 50.3, 65.6, 70.2, 115.5, 115.8, 121, 122.1, 126.6-(2C), 126.9, 127.6, 128.3, 128.9(2C), 129.1, 133.5, 139.5, 140.4, 147.4, 148.3, 164.5(2C). Anal. ($C_{24}H_{27}NO_2 \cdot C_2H_2O_4$) C, H, N.

2-(2-Isopropoxy-phenoxy)-ethyl]-(3-thien-2-yl-benzyl)-amine (5). Reductive amination between **IIIa** (0.38 g, 1.95 mmol) and **VIb** (0.36 g, 1.95 mmol) and then purification by flash column chromatography (silica gel, methylene chloride/methanol/ammonia, 95:4.5:0.5) gave 0.44 g (67%) of **5** as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.30 (d, J = 6 Hz, 6H), 3.05 (t, J = 5.2 Hz, 2H), 3.91 (s, 2H), 4.15 (t, J = 5.2 Hz, 2H), 4.45 (hept, J = 6 Hz, 1H), 6.89−6.93 (m, 4H), 7.07 (dd, J = 5.1, 3.7 Hz, 1H), 7.25−7.34 (m, 4H), 7.49 (d, J = 7.6 Hz, 1H), 7.60 (s, 1H). As the oxalate salt: white powder, mp = 195 °C; HPLC purity 99% (eluent, acetonitrile/water/KH_2PO_4, 400:600:6.8 g, pH 4); IR (KBr) ν 3410, 3038, 2852, 1701 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.22 (d, J = 6 Hz, 6H), 3.30 (t, J = 5.2 Hz, 2H), 4.24 (t, J = 5.2 Hz, 2H), 4.35 (s, 2H), 4.54 (hept, J = 6 Hz, 1H), 6.89 (dt, J = 7.5, 1.5 Hz, 1H), 6.94 (dt, J = 7.6, 1.5 Hz, 1H), 7.03 (dt, J = 6.5, 1.4 Hz, 2H), 7.16 (dd, J = 5, 3.7 Hz, 1H), 7.46−7.52 (m, 2H), 7.53 (dd, J = 3.5, 1 Hz, 1H), 7.58 (dd, J = 5, 1 Hz, 1H), 7.70 (d, J = 5 Hz, 1H), 7.83 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 21.8 (2C), 45.2, 50.3, 65.5, 70.2, 115.5, 115.8, 120.9, 122.1, 123.9, 125.6, 126, 126.9, 128.4, 128.9, 129.3, 133.7, 134, 142.7, 147.4, 148.3, 164.5 (2C). Anal. ($C_{22}H_{25}NO_2S \cdot C_2H_2O_4$) C, H, N.

2-(2-Isopropoxy-phenoxy)-ethyl]-(3-thien-3-yl-benzyl)-amine (6). Reductive amination between **IIIa** (0.35 g, 1.79 mmol) and **VIc** (0.34 g, 1.79 mmol) and then purification by flash column chromatography (silica gel, methylene chloride/methanol/ammonia, 95:4.5:0.5) afforded 0.47 g (71%) of **6** as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.19 (d, J = 6 Hz, 6H), 2.92 (t, J = 5.2 Hz, 2H), 3.80 (s, 2H), 4.05 (t, J = 5.2 Hz, 2H), 4.34 (hept, J = 6 Hz, 1H), 6.92−6.94 (m, 4H), 7.28−7.32 (m, 1H), 7.36−7.43 (m, 3H), 7.47−7.52 (m, 3H), 7.61 (s, 1H). As the oxalate salt: white powder, mp = 190 °C; HPLC purity 90% (eluent, acetonitrile/water/KH_2PO_4, 400:600:6.8 g, pH 4); IR (KBr) ν 2973, 1752, 1617, 1503 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.22 (d, J = 6 Hz, 6H), 3.29 (t, J = 5.1 Hz, 2H), 4.24 (t, J = 5.1 Hz, 2H), 4.34 (s, 2H), 4.56 (hept, J = 6 Hz, 1H), 6.89 (dt, J = 7.5, 1.4 Hz, 1H), 6.95 (dt, J = 7.6, 1.4 Hz, 1H), 7.03 (dt, J = 7, 1.4 Hz, 1H), 7.44−7.48 (m, 2H), 7.55 (dd, J = 5, 0.8 Hz, 1H), 7.67 (dd, J = 5, 3 Hz, 1H), 7.75 (d, J = 5 Hz, 1H), 7.86 (d, J = 3 Hz, 1H), 7.89 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 21.8 (2C), 45.1, 50.4, 65.5, 70.2, 115.5, 115.8, 120.9, 121.3, 122.1, 125.9, 126.3, 127.2, 127.6, 128.5, 129.1, 133.3, 135.4, 140.9, 147.4, 148.3, 164.6 (2C). Anal. ($C_{22}H_{25}NO_2S \cdot C_2H_2O_4$) C, H, N.

(3-Fur-2-yl-benzyl)-[2-(2-isopropoxy-phenoxy)-ethyl]-amine (7). Reductive amination between **IIIa** (0.32 g, 1.64 mmol) and **VId** (0.28 g, 1.64 mmol) and then purification by flash column chromatography (silica gel, methylene chloride/methanol/ammonia, 95:4.5:0.5) gave 0.32 g (56%) of **7** as a yellow oil: ^{1}H NMR (DMSO-d_6) δ 1.17 (d, J = 6 Hz, 6H), 2.86 (t, J = 5.6 Hz, 2H), 3.82 (s, 2H), 4.04 (t, J = 5.6 Hz, 2H), 4.45 (hept, J = 6 Hz, 1H), 6.58−6.60 (m, 1H), 6.85−6.89 (m, 2H), 6.91−6.95 (m, 2H), 6.97−6.99 (m, 1H), 7.26 (d, J = 7.6 Hz, 1H), 7.36 (dd, J = 7.7, 7.6 Hz, 1H), 7.57 (d, J = 7.7 Hz, 1H), 7.89 (s, 1H), 7.99 (s, 1H). As the oxalate salt: white powder, mp = 193 °C; HPLC purity 95.5% (eluent, acetonitrile/water/KH_2PO_4, 400:600:6.8 g, pH 4); IR (KBr) ν 3542, 3432, 2838, 1702, 1500 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.22 (d, J = 6 Hz, 6H), 3.30 (t, J = 4.5 Hz, 2H), 4.24 (t, J = 4.5 Hz, 2H), 4.35 (s, 2H), 4.56 (hept, J = 6 Hz, 1H), 6.62−6.64 (m, 1H), 6.73−6.90 (m, 1H), 6.93−7.05 (m, 4H), 7.43−7.53 (m, 2H), 7.74 (d, J = 7.5 Hz, 1H), 7.79 (s, 1H), 7.89 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 21.8 (2C), 45.2, 50.4, 65.5, 70.2, 106.3, 112.1, 115.4, 115.8, 120.9, 122.1, 123.6, 124.8, 128.8, 129.2, 130.6, 133.5, 143.1, 147.4, 148.3, 152.5, 164.5 (2C). Anal. ($C_{22}H_{25}NO_3 \cdot C_2H_2O_4$) C, H, N.

3-Cyclohept-1-enyl-benzyl)-[2-(2-isopropoxy-phenoxy)-ethyl]-amine (8). Reductive amination between **IIIa** (0.44 g, 2.23 mmol) and **VIe** (0.50 g, 2.23 mmol) and then purification by flash column chromatography (silica gel, methylene chloride/methanol/ammonia, 98:1.5:0.5) afforded 0.55 g (65%) of **8** as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.29 (d, J = 6.4 Hz, 6H), 1.52−1.56 (m, 2H), 1.62−1.65 (m, 2H), 1.78 (s, 1H), 1.80−1.85 (m, 2H), 2.25−2.30 (m, 2H), 2.58−2.62 (m, 2H), 3.03 (t, J = 5.2 Hz, 2H), 3.86 (s, 2H), 4.13 (t, J = 5.2 Hz, 2H), 4.41 (hept, J = 6.4 Hz, 1H), 6.09 (t, J = 6.8 Hz, 1H), 6.88−6.93 (m, 4H), 7.20−7.25 (m, 3H), 7.29 (s, 1H). As an oxalate salt: white powder, mp = 179 °C; HPLC purity 95.6% (eluent, acetonitrile/water/KH_2PO_4, 400:600:6.8 g, pH 4); IR (KBr) ν 3579, 3424, 2917, 1609, 1503 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.27 (d, J = 6 Hz, 6H), 1.54−1.57 (m, 2H), 1.59−1.63 (m, 2H), 1.81−1.89 (m, 2H), 2.22−2.29 (m, 2H), 2.55−2.62 (m, 2H), 3.30 (t, J = 5.2 Hz, 2H), 4.26 (t, J = 5.2 Hz, 2H), 4.27 (s, 2H), 4.51 (hept, J = 6 Hz, 1H), 6.08 (t, J = 6.5 Hz, 1H), 6.88−6.95 (m, 3H), 6.99−7.64 (m, 1H), 7.27−7.34 (m, 3H), 7.36 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 21.8(2C), 26.2, 26.3, 28.1, 31.8, 31.9, 45.1, 50.6, 65.5, 70.2, 115.4, 115.8, 120.9, 122.1, 125.6, 127, 127.9, 128.4, 130.4, 132.5, 143.8, 144.3, 147.4, 148.2, 164.3 (2C). Anal. ($C_{25}H_{33}NO_2 \cdot C_2H_2O_4$) C, H, N.

3-Cyclohex-1-enyl-benzyl)-[2-(2-isopropoxy-phenoxy)-ethyl]-amine (9). Reductive amination between **IIIa** (0.47 g, 2.56 mmol) and **VIf** (0.47 g, 2.56 mmol) and then purification by flash column chromatography (silica gel, methylene chloride/methanol/ammonia, 99:0.5:0.5) afforded 0.43 g (46%) of **9** as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.29 (d, J = 6 Hz, 6H), 1.63−1.68 (m, 2H), 1.74−1.80 (m, 2H), 2.17−2.21 (m, 2H), 2.38−2.42 (m, 2H), 3.03 (t, J = 5.2 Hz, 2H), 3.86 (s, 2H), 4.13 (t, J = 5.2 Hz, 2H), 4.42 (hept, J = 6.4 Hz, 1H), 6.10−6.12 (m, 1H), 6.91−6.93 (m, 4H), 7.18−7.21 (m, 1H), 7.25−7.27 (m, 3H), 7.38 (s, 1H). As an oxalate salt: white powder, mp = 165 °C; HPLC purity 97% (eluent, acetonitrile/water/KH_2PO_4, 400:600:6.8 g, pH 4); IR (KBr) ν 3435, 2926, 1702, 1495 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.22 (d, J = 6 Hz, 6H), 1.59−1.62 (m, 2H), 1.69−1.74 (m, 2H), 2.18−2.20 (m, 2H), 2.33−2.37 (m, 2H), 3.28 (t, J = 5.1 Hz, 2H), 4.25 (t, J = 5.1 Hz, 2H), 4.30 (s, 2H), 4.56 (hept, J = 6 Hz, 1H), 6.17−6.20 (m, 1H), 6.87−6.97 (m, 2H), 7.01−7.03 (m, 2H), 7.39−7.38 (m, 2H), 7.42−7.44 (m, 1H), 7.10 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 21.8, 21.7(2C), 22.4, 25.2, 26.6, 33.8, 45, 50.5, 65.4, 70.2, 115.4, 115.8, 120.9, 122.1, 124.9, 125, 126.3, 128.1, 128.5, 132.5, 135.4, 142.1, 147.4, 148.3, 164.5 (2C). Anal. ($C_{24}H_{31}NO_2 \cdot C_2H_2O_4$) C, H, N.

3-Cyclopent-1-enyl-benzyl)-[2-(2-isopropoxy-phenoxy)-ethyl]-amine (10). Reductive amination between **IIIa** (0.29 g, 1.49 mmol) and **VIg** (0.26 g, 1.49 mmol) and then purification by flash column chromatography (silica gel, methylene chloride/methanol/ammonia, 95:4.5:0.5) afforded 0.29 g (56%) of **10** as a colorless oil: ^{1}H NMR (DMSO-d_6) δ 1.20 (d, J = 6 Hz, 6H), 1.91−1.98 (m, 2H), 2.45−2.51 (m, 2H), 2.62−2.67 (m, 2H), 2.87 (t, J = 5.6 Hz, 2H), 3.77 (s, 2H), 4.03 (t, J = 5.6 Hz, 2H), 4.48 (hept, J = 6.4 Hz, 1H),

6.23−6.25 (m, 1H), 6.85−6.88 (m, 2H), 6.92−6.98 (m, 2H), 7.20 (d, J = 7.4 Hz, 1H), 7.26 (dd, J = 7.6, 7.4 Hz, 1H), 7.31 (d, J = 7.6 Hz, 1H), 7.42 (s, 1H). As an oxalate salt: white powder, mp = 191 °C; HPLC purity 97% (eluent, acetonitrile/water/KH_2PO_4, 400:600:6.8 g, pH 4); IR (KBr) ν 3051, 2973, 2848, 1723 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.22 (d, J = 6 Hz, 6H), 1.93−2.01 (m, 2H), 2.49−2.51 (m, 2H), 2.64−2.67 (m, 2H), 3.27 (t, J = 4.9 Hz, 2H), 4.24 (t, J = 4.9 Hz, 2H), 4.30 (s, 2H), 4.56 (hept, J = 6 Hz, 1H), 6.30−6.32 (m, 1H), 6.89 (dd, J = 7.4, 7.3 Hz, 1H), 6.95 (dd, J = 7.5, 6.9 Hz, 1H), 7.01−7.04 (m, 2H), 7.37−7.42 (m, 2H), 7.48−7.50 (m, 1H), 7.62 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 21.8 (2C), 22.7, 32.6, 32.8, 45, 50.5, 65.4, 70.2, 115.4, 115.8, 120.9, 122.1, 125.7, 126.7, 127, 128.4, 128.6, 132.7, 136.4, 141.5, 147.4, 148.3, 164.5 (2C). Anal. ($C_{23}H_{29}NO_2 \cdot C_2H_2O_4$) C, H, N.

3-Cyclopentanyl-benzyl)-[2-(2-isopropoxy-phenoxy)-ethyl]-amine (11). Reductive amination between **IIIa** (0.37 g, 1.88 mmol) and **VIh** (0.33 g, 1.88 mmol) and then purification by flash column chromatography (silica gel, methylene chloride/methanol/ammonia, 95:4.5:0.5) gave 0.51 g (77%) of **11** as a yellow oil: ^1H NMR (DMSO-d_6) δ 1.21 (d, J = 6 Hz, 6H), 1.51−1.53 (m, 2H), 1.62−1.65 (m, 2H), 1.73−1.76 (m, 2H), 1.97−2.00 (m, 2H), 2.84 (t, J = 5.7 Hz, 2H), 2.90−2.93 (m, 1H), 3.74 (s, 2H), 4.02 (t, J = 5.7 Hz, 2H), 4.45 (hept, J = 6.4 Hz, 1H), 6.81−6.87 (m, 2H), 6.92−6.98 (m, 2H), 7.07 (d, J = 7.5 Hz, 1H), 7.12 (d, J = 7.6 Hz, 1H), 7.18−7.32 (m, 2H). As an oxalate salt: white powder, mp = 178 °C; HPLC purity 98.3% (eluent, acetonitrile/water/KH_2PO_4, 400:600:6.8 g, pH 4); IR (KBr) ν 3416, 3052, 2955, 1721, 1501 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.22 (d, J = 6 Hz, 6H), 1.49−1.56 (m, 2H), 1.64−1.67 (m, 2H), 1.75−1.78 (m, 2H), 1.99−2.03 (m, 2H), 2.95−3.01 (m, 1H), 3.28 (t, J = 5.3 Hz, 2H), 4.23 (t, J = 5.2 Hz, 2H), 4.27 (s, 2H), 4.56 (hept, J = 6 Hz, 1H), 6.89−6.97 (m, 2H), 7.01 (d, J = 7.8 Hz, 2H), 7.01−7.04 (m, 2H), 7.27−7.34 (m, 3H), 7.40 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 21.8 (2C), 25 (2C), 34.1 (2C), 39, 45.1, 50.6, 65.4, 70.2, 115.4, 115.8, 120.9, 122.1, 127.2, 127.5, 128.4, 128.5, 132.5, 146.5, 147.4, 148.3, 164.5 (2C). Anal. ($C_{23}H_{31}NO_2 \cdot C_2H_2O_4$) C, H, N.

3-Cyclopropyl-benzyl)-[2-(2-isopropoxy-phenoxy)-ethyl]-amine (12). Reductive amination between **IIIa** (0.16 g, 0.79 mmol) and **VIi** (0.12 g, 0.79 mmol) and then purification by flash column chromatography (silica gel, methylene chloride/methanol/ammonia, 99:0.5:0.5) afforded 0.15 g (57%) of **12** as a pale yellow oil: ^1H NMR ($CDCl_3$) δ 0.68 (dd, J = 10.8, 5.2 Hz, 2H), 0.92 (dd, J = 13.6, 5.6 Hz, 2H), 1.31 (d, J = 6 Hz, 6H), 1.84−1.92 (m, 1H), 3.03 (t, J = 5.2 Hz, 2H), 3.84 (s, 2H), 4.11 (t, J = 5.2 Hz, 2H), 4.44 (hept, J = 6 Hz, 1H), 6.93−6.99 (m, 5H), 7.07 (s, 1H), 7.12 (d, J = 7.6 Hz, 1H), 7.21 (dd, J = 7.6, 7.5 Hz, 1H). As an hemifumarate salt: white powder, mp = 99 °C; HPLC purity 97.8% (eluent, acetonitrile/water/KH_2PO_4, 400:600:6.8 g, pH 4); IR (KBr) ν 3414, 2976, 1709, 1618, 1499 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.60−0.67 (m, 2H), 0.91−0.96 (m, 2H), 1.22 (d, J = 6 Hz, 6H), 1.86−1.92 (m, 1H), 2.95 (t, J = 5.6 Hz, 2H), 3.88 (s, 2H), 4.08 (t, J = 5.6 Hz, 2H), 4.5 (hept, J = 6 Hz, 1H), 6.56 (s, 2.4H), 6.87−6.9 (m, 2H), 6.97−7.03 (m, 3H), 7.09 (s, 1H), 7.13 (d, J = 7.4 Hz, 1H), 7.21 (dd, J = 7.5, 7.4 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 9.3 (2C), 14.8, 21.8 (2C), 45.7, 51.1, 66.5, 70.4, 115.2, 116.3, 121.1, 121.7, 125.1, 126, 126.1, 128.2, 134.6 (2C), 135.3, 143.9, 147.3, 148.7, 167.1 (2C). Anal. ($C_{21}H_{27}NO_2 \cdot 1.2C_4H_4O_4$) C, H, N.

(3-Cyclopent-1-enyl-benzyl)-[2-(2,3-dihydro-benzo[1,4]dioxin-5-yloxy)-ethyl]-amine (13). Reductive amination between **IIIb** (0.50 g, 2.56 mmol) and **VIg** (0.44 g, 2.56 mmol) and then purification by flash column chromatography (silica gel, methylene chloride/methanol/ammonia, 95:4.5:0.5) gave 0.49 g (55%) of **13** as a yellow oil: ^1H NMR ($CDCl_3$) δ 1.85 (s, 1H), 1.85−2.05 (m, 2H), 2.50−2.55 (m, 2H), 2.68−2.73 (m, 2H), 3.05 (t, J = 5.6 Hz, 2H), 3.87 (s, 2H), 4.14 (t, J = 5.6 Hz, 2H), 4.23−4.27 (m, 2H), 4.28−4.32 (m, 2H), 6.18−6.20 (m, 1H), 6.54 (d, J = 8.2 Hz, 1H), 6.55 (d, J = 8.3 Hz, 1H), 6.74 (d, J = 8.2, 8.3 Hz, 1H), 7.19 (d, J = 7.4 Hz, 1H), 7.24−7.28 (m, 1H), 7.31 (d, J = 7.6 Hz, 1H), 7.47 (s, 1H). As a fumarate salt: white powder, mp = 138 °C; HPLC purity 99.4% (eluent, acetonitrile/water/KH_2PO_4, 350:650:6.8 g, pH 4); IR (KBr) ν 3500, 2842, 1594, 1501, 1332, 1117 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.92−1.99 (m, 2H), 2.32−2.51 (m, 2H), 2.63−2.68 (m, 2H), 2.98 (t, J = 5.6 Hz, 2H), 3.93 (s, 2H), 4.21 (t, J = 5.6 Hz, 2H), 4.22 (s, 4H), 6.27−6.28 (m, 1H), 6.47 (dd, J = 8.2, 1 Hz, 1H), 6.55−6.58 (m, 2H), 6.69 (dd, J = 8.3, 8.2 Hz, 1H), 7.25−7.38 (m, 2H), 7.37 (d, J = 7.5 Hz, 1H), 7.51 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 22.7, 32.6, 32.8, 45.9, 51.3, 63.7, 63.8, 66.5, 106.2, 110.1, 119.8, 124.8, 126.2, 126.3, 127.6, 128.3, 133.6, 134.7 (2C), 136.2, 141.7, 144, 147.5, 167.3 (2C). Anal. ($C_{22}H_{25}NO_3 \cdot C_4H_4O_4$) C, H, N.

[2-(Benzo[1,3]dioxol-4-yloxy)-ethyl]-(3-cyclopent-1-enyl-benzyl)-amine (14). Reductive amination between **IIIc** (0.27 g, 1.34 mmol) and **VIg** (0.23 g, 1.34 mmol) and then purification by flash column chromatography (silica gel, methylene chloride/methanol/ammonia, 98:1.5:0.5) afforded 0.40 g (89%) of **14** as a yellow oil: ^1H NMR ($CDCl_3$) δ 1.97−2.05 (m, 2H), 2.17 (s, 1H), 2.50−2.55 (m, 2H), 2.69−2.73 (m, 2H), 3.02 (t, J = 5.2 Hz, 2H), 3.86 (s, 2H), 4.21 (t, J = 5.2 Hz, 2H), 5.91−5.96 (m, 2H), 6.15−6.20 (m, 1H), 6.52 (d, J = 8.2 Hz, 1H), 6.75 (t, J = 8.2 Hz, 1H), 7.19 (d, J = 7.4 Hz, 1H), 7.26−7.28 (m, 1H), 7.33 (d, J = 7.6 Hz, 1H), 7.47 (s, 1H). As a fumarate salt: white powder, mp = 133 °C; HPLC purity 97.4% (eluent, acetonitrile/water/KH_2PO_4, 350:650:6.8 g, pH 4); IR (KBr) ν 2949, 2843, 1637, 1464 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.94−1.99 (m, 2H), 2.33−2.51 (m, 2H), 2.64−2.67 (m, 2H), 2.96 (t, J = 5.6 Hz, 2H), 3.89 (s, 2H), 4.19 (t, J = 5.6 Hz, 2H), 5.96 (s, 2H), 6.27 (s, 1H), 6.57 (s, 2H), 6.60−6.64 (m, 2H), 6.78 (dd, J = 8.1, 8.2, 1H), 7.25 (dd, J = 9.3, 7.4 Hz, 1H), 7.30 (d, J = 7.5 Hz, 1H), 7.37 (d, J = 7.6 Hz, 1H), 7.49 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 22.7, 32.6, 32.8, 46, 51.2, 66.7, 100.8, 102.5, 109.2, 122, 124.8, 126.2, 126.3, 127.6, 128.3, 124.6, 135 (2C), 136, 136.2, 141.7, 142.3, 148.4, 167 (2C). Anal. ($C_{21}H_{23}NO_3 \cdot C_4H_4O_4$) C, H, N.

(3-Cyclopent-1-enyl-benzyl)-[2-(2,2-dimethyl-benzo[1,3]dioxol-4-yloxy)-ethyl]-amine (15). Reductive amination between **IIId** (0.64 g, 3.06 mmol) and **VIg** (0.53 g, 3.06 mmol) and then purification by flash column chromatography (silica gel, methylene chloride/methanol/ammonia, 95:4.5:0.5) afforded 0.76 g (68%) of **15** as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.67 (s, 6H), 1.99−2.05 (m, 2H), 2.50−2.55 (m, 2H), 2.69−2.73 (m, 2H), 3.02 (t, J = 5.2 Hz, 2H), 3.85 (s, 2H), 4.21 (t, J = 5.2 Hz, 2H), 6.19−6.20 (m, 1H), 6.44 (d, J = 7.8 Hz, 1H), 6.49 (d, J = 8.3 Hz, 1H), 6.70 (dd, J = 8.2, 8.1 Hz, 1H), 7.19 (d, J = 7.4 Hz, 1H) 7.25−7.35 (m, 2H), 7.41 (s, 1H). As a fumarate salt: white powder, mp = 150 °C; HPLC purity 95.3% (eluent, acetonitrile/water/KH_2PO_4, 350:650:6.8 g, pH 4); IR (KBr) ν 3589, 1631, 1501, 1466 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.61 (s, 1H), 1.77−1.99 (m, 2H), 2.48−2.51 (m, 2H), 2.63−2.67 (m, 2H), 2.92 (t, J = 5.6 Hz, 2H), 3.84 (s, 2H), 4.12 (t, J = 5.6 Hz, 2H), 6.26 (s, 1H), 6.48 (d, J = 8.2 Hz, 1H), 6.6 (s, 2H), 6.61 (d, J = 6.5 Hz, 1H), 6.71 (dd, J = 8.21, 8, 1H), 7.23 (d, J = 7.4 Hz, 1H), 7.29 (dd, J = 7.5, 7.3 Hz, 1H), 7.34 (d, J = 7.6 Hz, 1H), 7.46 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 22.7, 25.4 (2C), 32.6, 32.8, 46.2, 51.4, 66.7, 102.3, 108.5, 117.9, 121.3, 124.7, 126.1, 126.2, 127.6, 128.3, 134.6, 134.7 (2C), 136.1, 136.5, 141.7, 142.2, 147.9, 167.1 (2C). Anal. ($C_{23}H_{27}NO_3 \cdot C_4H_4O_4$) C, H, N.

(3-Cyclopent-1-enyl-benzyl)-[2-(2,2-dimethyl-2,3-dihydro-benzofuran-7-yloxy)-ethyl]-amine (16). Reductive amination between **IIIe** (4.80 g, 0.023 mol) and **VIg** (4 g, 0.023 mol) and then purification by flash column chromatography (silica gel, methylene chloride/methanol/ammonia, 95:4.5:0.5) afforded 7.35 g (88%) of **16** as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.47 (s, 3H), 1.50 (s, 3H), 1.91−1.98 (m, 2H), 2.45−2.51 (m, 2H), 2.62−2.67 (m, 2H), 3.04 (t, J = 5.6 Hz, 2H), 3.85 (s, 2H), 4.18 (t, J = 5.6 Hz, 2H), 6.18 (s, 1H), 6.74 (m, 3H), 7.19 (d, J = 7.4 Hz, 1H), 7.25 (t, J = 8.7 Hz, 1H), 7.32 (d, J = 7.6 Hz, 1H), 7.41 (s, 1H). As a fumarate salt: white powder, mp = 139 °C; HPLC purity 99.1% (eluent, acetonitrile/water/KH_2PO_4, 350:650:6.8 g, pH 4); IR (KBr) ν 3060, 2967, 1719, 1463 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.39 (s, 6H), 1.94−1.97 (m, 2H), 2.50−2.55 (m, 2H), 2.60−2.69 (m, 2H), 2.96 (t, J = 5.6 Hz, 2H), 2.99 (s, 2H), 3.91 (s, 2H), 4.11 (t, J = 5.6 Hz, 2H), 6.27 (s, 1H), 6.56 (s, 2H), 6.70−6.74 (m, 1H), 6.77−6.80 (m, 2H), 7.28−7.33 (m, 2H), 7.37 (d, J = 7.6 Hz, 1H), 7.50 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 22.7, 27.8 (2C), 32.6, 32.8, 42.4, 46, 51.2,

66.3, 86.9, 113.6, 118, 120.2, 124.8, 126.2, 126.3, 127.7, 128.3, 128.4, 134.7 (2C), 136, 136.2, 141.7, 142.7, 147.1, 167.3 (2C). Anal. ($C_{24}H_{29}NO_2 \cdot C_4H_4O_4$) C, H, N.

(3-Cyclopenten-1-yl-benzyl)-[2-(2-spiro-cyclopropyl-2,3-dihydro-benzofuran-7-yloxy)-ethyl]-amine (17). Reductive amination between **IIIf** (0.30 g, 1.46 mmol) and **VIg** (0.25 g, 1.46 mmol) and then purification by flash column chromatography (silica gel, methylene chloride/methanol/ammonia, 95:4.5:0.5) gave 0.45 g (86%) of **17** as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.69 (t, J = 6.4 Hz, 2H), 1.22 (t, J = 6.4 Hz, 2H), 1.23 (s, 1H), 2.00−2.03 (m, 2H), 2.49−2.25 (m, 2H), 2.68−2.71 (m, 2H), 3.01 (t, J = 5.2 Hz, 2H), 3.31 (s, 2H), 3.84 (s, 2H), 4.17 (t, J = 5.2 Hz, 2H), 6.18 (s, 1H), 6.79−6.84 (m, 3H), 7.18 (d, J = 7.4 Hz, 1H), 7.25 (t, J = 7.6 Hz, 1H), 7.31 (d, J = 7.6 Hz, 1H), 7,40 (s, 1H). As a maleate salt: white powder, mp = 180 °C; HPLC purity 98.3% (eluent, acetonitrile/water/KH_2PO_4, 400:600:6.8 g, pH 4); IR (KBr) ν 3454, 2998, 2957, 2841, 1621, 1461 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 0.78 (t, J = 6.4 Hz, 2H), 1.06 (t, J = 6.4 Hz, 2H), 1.96−1.99 (m, 2H), 2.49−2.52 (m, 2H), 2.66−2.68 (m, 2H), 3.30−3.33 (m, 4H), 4.21−4.24 (m, 4H), 6.02 (s, 2H), 6.32 (s, 1H), 6.81−6.84 (m, 3H), 7.36−7.38 (m, 2H), 7.51 (d, J = 7.6 Hz, 1H), 7.60 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 11.7 (2C), 22.7, 32.6, 32.9, 35.7, 45.5, 50.5, 64.8, 67.9, 113.8, 118.2, 121, 125.9, 126.8, 127.1, 128.3, 128.5, 128.7, 131.9, 135.9 (2C), 136.4, 141.4, 142.1, 147.8, 167.1 (2C). Anal. ($C_{24}H_{27}NO_2 \cdot C_4H_4O_4$) C, H, N.

(3-Cyclopent-1-enyl-benzyl)-[2-(2-ethyl-2-methyl-2,3-dihydro-benzofuran-7-yloxy)-ethyl]-amine (18). Reductive amination between **IIIg** (0.68 g, 3.07 mmol) and **VIg** (0.53 g, 3.07 mmol) and then purification by flash column chromatography (silica gel, methylene chloride/methanol/ammonia, 95:4.5:0.5) afforded 0.42 g of **18** as a yellow oil (36%): ^{1}H NMR ($CDCl_3$) δ 0.95 (t, J = 7.6 Hz, 2H), 1.42 (s, 3H), 1.77 (q, J = 7.6 Hz, 2H), 1.97−2.05 (m, 2H), 2.50−2.54 (m, 2H), 2.68−2.73 (m, 2H), 2.98 (ABq, $\Delta\nu_{AB}$ = 68.8 Hz, J = 15.2 Hz, 2H), 3.02 (t, J = 5.2 Hz, 2H), 4.16 (t, J = 5.2 Hz, 2H), 5.3 (s, 1H), 6.70−6.76 (m, 3H), 7.14 (d, J = 7.2 Hz, 1H), 7.25 (t, J = 7.7 Hz, 1H), 7.32 (d, J = 7.6 Hz, 1H), 7.40 (s, 1H). As a fumarate salt: white powder, mp = 108 °C; HPLC purity 95.1% (eluent, acetonitrile/water/KH_2PO_4, 350:650:6.8 g, pH 4); IR (KBr) ν 3431, 2966, 1706, 1593 cm^{-1}; ^{1}H NMR (DMSO-d_6) 0.88 (t, J = 7.2 Hz, 3H), 1.33 (s, 3H), 1.65−1.72 (m, 2H), 1.94−1.99 (m, 2H), 2.50−2.55 (m, 2H), 2.65 (q, J = 6.8 Hz, 2H), 2.97 (ABq, $\Delta\nu_{AB}$ = 60.8 Hz, J = 15.6 Hz, 2H), 2.93 (t, J = 5.6 Hz, 2H), 3.88 (s, 2H), 4.10 (t, J = 5.6 Hz, 2H), 6.26 (s, 1H), 6.57 (s, 2H), 6.70 (t, J = 8 Hz, 1H), 6.77−6.79 (m, 2H), 7.16−7.31 (m, 2H), 7.35 (d, J = 7.4 Hz, 1H), 7.47 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 8.2, 22.7, 25.6, 32.6, 32.8, 33.1, 39.4, 46, 51.2, 66.5, 89.4, 113.8, 118, 120.1, 124.8, 126.1, 126.2, 127.7, 128.3, 128.4, 134.6 (2C), 136.1, 136.2, 141.7, 142.5, 147.4, 167 (2C). Anal. ($C_{25}H_{31}NO_2 \cdot C_4H_4O_4$) C, H, N.

(3-Cyclopent-1-enyl-benzyl)-[2-(3,3-dimethyl-2,3-dihydro-benzofuran-7-yloxy)-ethyl]-amine (19). Reductive amination between **IIIh** (0.60 g, 2.89 mmol) and **VIg** (0.50 g, 2.89 mmol) and then purification by flash column chromatography (silica gel, methylene chloride/methanol/ammonia, 98:1.5:0.5) afforded 0.86 g (82%) of **19** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 6H), 1.98−2.05 (m, 2H), 2.50−2.54 (m, 2H), 2.69−2.73 (m, 2H), 3.05 (t, J = 5.2 Hz, 2H), 3.83 (s, 2H), 4.18 (t, J = 5.2 Hz, 2H), 4.26 (s, 2H), 6.07−6.09 (m, 1H), 6.71−6.77 (m, 2H), 7.02 (t, J = 7.9 Hz, 1H), 7.19 (d, J = 7.4 Hz, 1H), 7.24 (dd, J = 7.6, 7.4 Hz, 1H), 7.33 (d, J = 7.6 Hz, 1H), 7.42 (s, 1H). As a fumarate salt: white powder, mp = 139 °C; HPLC purity 97.9% (eluent, acetonitrile/water/KH_2PO_4, 450:550:6.8 g, pH 4); IR (KBr) ν 3441, 2959, 2893, 1705, 1618 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.27 (s, 6H), 1.92−1.99 (m, 2H), 2.46−2.51 (m, 2H), 2.63−2.68 (m, 2H), 2.99 (t, J = 5.6 Hz, 2H), 3.49 (s, 2H), 4.15 (t, J = 5.6 Hz, 2H), 4.19 (s, 2H), 6.27−6.28 (m, 1H), 6.56 (s, 2H), 6.74−6.84 (m, 3H), 7.27 (d, J = 7.4 Hz, 1H), 7.31 (t, J = 7.4 Hz, 1H), 7.38 (d, J = 7.4 Hz, 1H), 7.52 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 22.7, 27 (2C), 32.6, 32.8, 41.8, 46, 51.3, 66.3, 83.8, 113.4, 115.1, 121.1, 124.8, 126.2, 126.2, 127.6, 128.3, 134.6 (2C), 136.1, 136.2, 138, 141.7, 142.7, 146.9, 167.2 (2C). Anal. ($C_{24}H_{29}NO_2 \cdot C_4H_4O_4$) C, H, N.

(5-Cyclopent-1-enyl-pyridin-3-yl-methyl)-[2-(2,2-dimethyl-2,3-dihydro-benzofuran-7-yloxy)-ethyl]-amine (20). Reductive amination between **IIIe** (0.77 g, 3.71 mmol) and **VIj** (0.64 g, 3.71 mmol) and then purification by flash column chromatography (silica gel, methylene chloride/methanol/ammonia, 98:1.5:0.5) gave 1.17 g (87%) of **20** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.74 (s, 6H), 2.02−2.07 (m, 2H), 2.50−2.56 (m, 2H), 2.69−2.71 (m, 2H), 3.01−3.04 (m, 4H), 3.86 (s, 2H), 4.19 (t, J = 5.2 Hz, 2H), 6.28 (s, 1H), 6.74−6.77 (m, 3H), 7.71 (s, 1H), 8.49 (s, 1H), 8.57 (s, 1H). As a maleate salt: white powder, mp = 169 °C; HPLC purity 99.9% (eluent, acetonitrile/water/KH_2PO_4, 350:650:6.8 g, pH 4); IR (KBr) ν 3434, 3038, 2971, 1621, 1577, 1463 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.41 (s, 6H), 1.96−2.04 (m, 2H), 2.49−2.51 (m, 2H), 2.68−2.71 (m, 2H), 3.01 (s, 2H), 3.34−3.57 (m, 4H), 4.25 (t, J = 4.8 Hz, 2H), 4.30 (s, 2H), 6.02 (s, 2H), 6.42 (m, 1H), 6.77 (dd, J = 7.7, 7.6 Hz, 1H), 6.84 (dd, J = 6.9, 1.6 Hz, 1H), 7.99 (s, 1H), 8.55 (s, 1H), 8.81 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 22.6, 27.8 (2C), 32.3, 33, 42.3, 45.9, 47.9, 64.9, 87.2, 113.9, 118.6, 120.3, 127.6, 128.7, 128.9, 131.2, 134.2, 135.9 (2C), 138.6, 142.3, 147, 147.1, 149.1, 167.1 (2C). Anal. ($C_{23}H_{28}N_2O_2 \cdot C_4H_4O_4$) C, H, N.

(5-Cyclopent-1-enyl-pyridin-3-ylmethyl)-[2-(2-spiro-cyclopropyl-2,3-dihydro-benzofuran-7-yloxy)]-ethylamine (21). Reductive amination between **IIIf** (0.44 g, 2.17mmol) and **VIj** (0.38 g, 2.17 mmol) and then purification by flash column chromatography (silica gel, methylene chloride/methanol/ammonia, 95:4.5:0.5) delivered 0.60 g (76%) of **21** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.69 (t, J = 6.8 Hz, 2H), 1.23 (t, J = 6.4 Hz, 2H), 2.00−2.08 (m, 2H), 2.53−2.62 (m, 2H), 2.69−2.74 (m, 2H), 3.01 (t, J = 5.2 Hz, 2H), 3.31 (s, 2H), 3.85 (s, 2H), 4.17 (t, J = 5.2 Hz, 2H), 6.28 (s, 1H), 6.78−6.84 (m, 3H), 7.70 (s, 1H), 8.39 (s, 1H), 8.57 (s, 1H). As a fumarate salt: white powder, mp = 162 °C; HPLC purity 96.3% (eluent, acetonitrile/water/KH_2PO_4, 350:650:6.8 g, pH 4); IR (KBr) ν 3434, 2958, 285, 1729, 1642 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 0.75 (t, J = 6.4 Hz, 2H), 1.07 (t, J = 6.4 Hz, 2H), 1.94−2.01 (m, 2H), 2.49−2.51 (m, 2H), 2.65−2.70 (m, 2H), 2.92 (t, J = 5.6 Hz, 2H), 3.29 (s, 2H), 3.87 (s, 2H), 4.10 (t, J = 5.6 Hz, 2H), 6.41 (s, 1H), 6.60 (s, 2H), 6.78−6.85 (m, 3H), 8.41 (d, J = 1.4 Hz, 1H), 8.60 (d, J = 1.8 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 11.8 (2C), 22.7, 32.3, 32.9, 35.8, 47, 49.6, 67.7, 67.8, 87.2, 113, 117.3, 121, 127.9, 128, 131.1, 132.3, 134.3 (2C), 134.6, 139.1, 142.9, 145.3, 147.7, 147.9, 166.4 (2C). Anal. ($C_{24}H_{27}NO_2 \cdot C_4H_4O_4$) C, H, N.

Radioligand Binding. The membrane preparations and binding assays were performed as described previously: 5-HT_{1A}, D_2,[52] and 5-HT_{2A}.[53] The binding parameters are summarized in Table 4. At the end of the incubation period, the tube contents were filtered under vacuum through GF/B filters with two 5 mL washes of Tris-HCl buffer (50 mM, pH 7.4 at 25 °C). The radioactivity retained on the filters was measured by scintillation spectroscopy in 4 mL of scintillation fluid (emulsifier safe, Packard). The results of displacement experiments were analyzed using the nonlinear regression program KELL RADLIG version 6 (Biosoft, Cambridge, U.K.),[54] and pK_i values are given as means ± SEM of three experiments, each comprising 6−7 concentrations differing by one log unit interval. The −log of K_i values (pK_i) were calculated from the Cheng−Prusoff equation $K_i = IC_{50}/(1 + [\text{radioligand}]/K_d)$. The K_d values of the different ligands are reported in Table 4. [^{3}H]8-OH-DPAT (TRK.850: 160−240 Ci/mmol) was purchased from Amersham; [^{3}H]ketanserin (NET-791: 60−90 Ci/mmol) and [^{3}H]-YM-09151−2 (NET-1004: 70−87 Ci/mmol) from NEN; 5-HT from Sigma; methysergide maleate and (+)-butaclamol hydrochloride from RBI.

[^{35}S]GTPγS Binding in HeLa Cells. The membrane preparations and binding assays were performed as described previously.[55] Cells were harvested in ice-cold 20 mM Hepes buffer containing EDTA (10 mM, pH 7.4) at rt and were homogenized and centrifuged at 40 000 g at 4 °C for 15 min. The pellet was suspended in ice-cold 20 mM Hepes containing EDTA (0.1 mM) and centrifuged at 40 000 g at 4 °C for 15 min. The final pellet was suspended in 20 mM Hepes containing $MgCl_2$ (10 mM), pargyline (10 μM), GDP (30 μM), and NaCl (100 mM). The membranes (100−50 μg/tube) were incubated in the presence of the test

compounds for 1 h at 30 °C. After 15 min at 0 °C, [^{35}S]GTPγS (specific activity ≈ 1100 Ci/mmol) was added to a final concentration of 0.1 nM. The membranes were then incubated for an additional 30 min at 30 °C. The reaction was terminated by filtration through Whatman filters using a Brandel harvester, and radioactivity was counted by liquid scintillation spectrometry. Compounds were tested at six concentrations from 10^{-10} M to 10^{-5} M. Concentration effect is expressed as −log(M) of the test compound versus % of basal [^{35}S]GTPγS binding. Values are expressed as % of the stimulation obtained with 5-HT (10^{-5} M) according to the following formula: % stimulation = [(E_{max}compound − 100)/(E_{max}5-HT − 100)100]. Each concentration−response experiment was performed in triplicate and replicated three times. Each concentration−response experiment included 5-HT (10^{-5} M). The pEC_{50} values were estimated using the mean values of three separate experiments by means of nonlinear regression using the program GraphPad Prism. [^{35}S]GTPγS (1100 Ci/mmol) was obtained from Amersham (Les Ulis, France); 5-HT was obtained from Sigma (St Louis, U.S.A.).

Behavioral Effects Induced by 5-HT$_{1A}$ Agonists. The method used was similar to those described previously.[56] Behavioral observations were made at 15 min after the injection, each lasting for a total of 10 min. The animals were observed individually during the 10 min period. During each of these observation periods, the presence (1) or absence (0) of LLR was recorded. The LLR was considered present if the animal showed uninterrupted signs for at least 3 s. This cycle was repeated 10 times during a 10 min period; the incidence of a particular behavior could vary from 0 to 10 for any observation period. An injection volume of 10 mL/kg was used throughout, and doses refer to the weight of the free base. Compounds were tested in five animals per dose. Dose−response functions were determined from the percentage of rats showing LLR scores of 1 or more. These criteria were based upon the incidence of each particular behavior observed in saline-treated animals. ED_{50} values and their 95% confidence limits were calculated by Litchfield and Wilcoxon probit analysis.[57] FBP was scored present (1) if it occurred during the entire observation period, otherwise, the score was 0. On each day, only two animals in each group received the same dose of the same drug.

Methylphenidate-Induced Behaviors. The observational method used has been described previously.[42a] Observations were made during a 10 min period starting 30 min after the injection of the drug using subgroups of four animals. Each min each of the four rats was successively observed during a 10 s period (i.e., one animal every 15 s) for the presence or absence of locomotion, rearing, sniffing, gnawing, licking, and for the occurrence of the other directly observable phenomena. This cycle was repeated 10 times during a 10 min period; the incidence of a particular behavior could vary from 0 to 10 for the entire observation period. An injection volume of 10 mL/kg was used throughout and doses refer to the weight of the free base. Compounds were tested in seven animals per dose.

Drug effects on methylphenidate-induced behaviors were evaluated based upon the incidence of each particular behavior observed in control animals treated with saline or with 40 mg/kg methylphenidate; dose−response functions were determined from the percentage of rats showing normalization. ED_{50} values and their 95% confidence limits and potency ratios were calculated by Litchfield and Wilcoxon probit analysis.[57]

Crossed-Leg Position Test. Animals were injected with the compound to be tested and the catalepsy procedure began 60 min after injection.[42b] Animals were examined in the cross-legged position test; the hind limbs were placed over the ipsilateral forelimbs, and the time during which the animal remained in this position was determined up to a maximum of 30 s. The test was repeated 3 and 6 min later, and the mean of the three trials was used for analysis. Animals were returned to their home cage between tests. Seven animals were tested under each treatment condition. An injection volume of 10 mL/kg was used throughout, and doses refer to the weight of the free base. Compounds were tested in seven animals per dose.

The measures used in this study were the mean duration values for catalepsy in the cross-legged position and the percentage incidence of catalepsy defined as one or more observations of catalepsy lasting 30 s in an individual animal. Dose−response functions were determined from the percentage of rats showing a duration of catalepsy for at least 30 s. ED_{50} values and their 95% confidence limits were calculated by Litchfield and Wilcoxon probit analysis.[57]

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Supporting Information Available: Experimental and analytical data for intermediates: **If**−**h**, **IIc**−**h**, corresponding Gabriel's adducts, **IVe**−**g**, and **V**; pK_b and E_{max} values for compounds **1**, **16**, **20**, and haloperidol. This material is available free of charge via the Internet at http://pubs.acs.org.

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