New Benzocycloalkylpiperazines, Potent and Selective 5-HT$_{1A}$ Receptor Ligands

Youssef El Ahmad,[†] Elisabeth Laurent,[†] Philippe Maillet,[†] Akram Talab,[†] Jean François Teste,[†] Raymond Dokhan,[‡] Gilles Tran,[†] and Roland Ollivier*,[†]

Centre de Recherche, Cooperation Pharmaceutique Française, 13-15, rue Benjamin Franklin, 77000 La Rochette, France, and Laboratoire LDK France, Les Algorythmes, Batiment Aristote, Saint Aubin, 91194, Gif sur Yvette, France

Received October 12, 1995[⊗]

A series of 1-(benzocycloalkyl)-4-(benzamidoalkyl)piperazine derivatives was prepared in order to obtain compounds with a high affinity and selectivity for 5-HT$_{1A}$ receptors. The modifications of aromatic substituents, the length of the alkyl chain, and the size of the ring were explored. Most of *N*-(1,2,3,4-tetrahydronaphthyl)-*N′*-(benzamidoethyl)piperazines (**32**−**37**) were bound to 5-HT$_{1A}$ receptors in a nanomolar range and presented a high degree of selectivity. After resolution, levorotatory enantiomers showed affinity and selectivity higher than those of dextrorotatory ones for 5-HT$_{1A}$ sites. The agonist type activity of selected derivatives was also confirmed *in vitro* on the inhibition of the activation of adenylate cyclase induced by forskolin and, *in vivo*, on the induction of the lower lip retraction in rats.

Introduction

Serotonin is a neuromediator well-known for its implication in mood regulation, anxiety, depression, and insomnia.[1−3] It was proved that the increase in its bioavailability, as seen with specific reuptake inhibitors,[4] such as fluoxetine (Chart 1), made it possible to treat depressive symptoms. The discovery of several classes of receptors for serotonin and the search for their implications in the mechanisms of mood and anxiety have been widely studied. Today four types of receptors have been identified, 5-HT$_1$, 5-HT$_2$, 5-HT$_3$, and 5-HT$_4$, and in the 5-HT$_1$ group, four subtypes, 5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{1C}$, and 5-HT$_{1D}$ have been found.[5,6] One of these receptor subtypes, the 5-HT$_{1A}$ one, is found in high concentrations in the limbic system in which it is thought to play a role in emotional processes.[7] The activation of the 5-HT$_{1A}$ receptor leads to a number of physiological changes that can be easily quantified. For example, the administration of 5-HT$_{1A}$ agonists can result in a temperature decrease,[8] an increase in serum corticosterone,[9] an inhibition of firing of 5-HT-containing neurons,[10] and a characteristic set of motor changes collectively known as the serotonin motor syndrome.[11] The synthesis of a specific 5-HT$_{1A}$ receptor ligand, the 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT),[12] and the study of its pharmacological properties showed that agonists inhibited 5-HT function and release, which is a potentially important event for the treatment of anxiety states. Several structurally different compounds possessed high affinity and selectivity for 5-HT$_{1A}$ receptors.[13] Among these some piperazine compounds such as buspirone,[14] gepirone,[15] tandospirone[16] or ipsapirone[17] showed selective agonist or partial agonist activity for 5-HT$_{1A}$ receptors and have proved to be effective for the treatment of anxiety states or depression. The search for new selective 5-HT$_{1A}$ receptor agonists has yielded active compounds (Chart 1). During the recent years, serotoninergic 5-HT$_{1A}$ ligands have been suggested to be useful as therapies for anxiety,[18,19] depression,[20] nausea and vomiting,[21,22] Alzheimer's disease,[23] prostate cancer,[24] hypertension, pain,[25,26] or alcoholism.[27−30] Today buspirone (Buspar) is the only compound commercialized for the treatment of anxiety

In the past, we studied a new piperazinotetralyl derivative, MB 35,[31] which possessed, *in vivo*, the same pharmacological profile as that of buspirone. Binding studies showed that this compound had a good affinity for adrenergic α_1 (K_i = 18 nM) and serotoninergic 5-HT$_{1A}$ (K_i = 17 nM) receptors, an intermediate affinity for histaminergic H$_1$ (K_i = 42 nM), serotoninergic 5-HT$_2$ (K_i = 66 nM), and dopaminergic D$_2$ (K_i = 109 nM) receptors, and a low affinity for serotoninergic 5-HT$_3$, dopaminergic D$_1$, β-adrenergic, muscarinic M$_1$, M$_2$, benzodiazepinic, and GABA receptors. MB 35 was a nonselective 5-HT$_{1A}$ ligand. We postulated that D$_2$ and 5-HT$_2$ affinities were carried by the (4-fluorophenyl)-butyrophenone moiety which is also present in haloperidol, a D$_2$ receptor antagonist. We replaced the butyrophenone group by a benzamidoalkyl group to try to obtain selective 5-HT$_{1A}$ agonists. In this work we studied the affinity and the selectivity of new (benzocycloalkyl)piperazines (**I**) for 5-HT$_{1A}$ receptor in relation to the structural modifications such as the benzocycloalkyl size (*m*), the length of the aliphatic chain (n), the nature of the substituents on the benzamide moiety (R$_1$, R$_2$, R$_3$), and the stereochemistry of the benzocycloalkyl moiety.

Chemistry

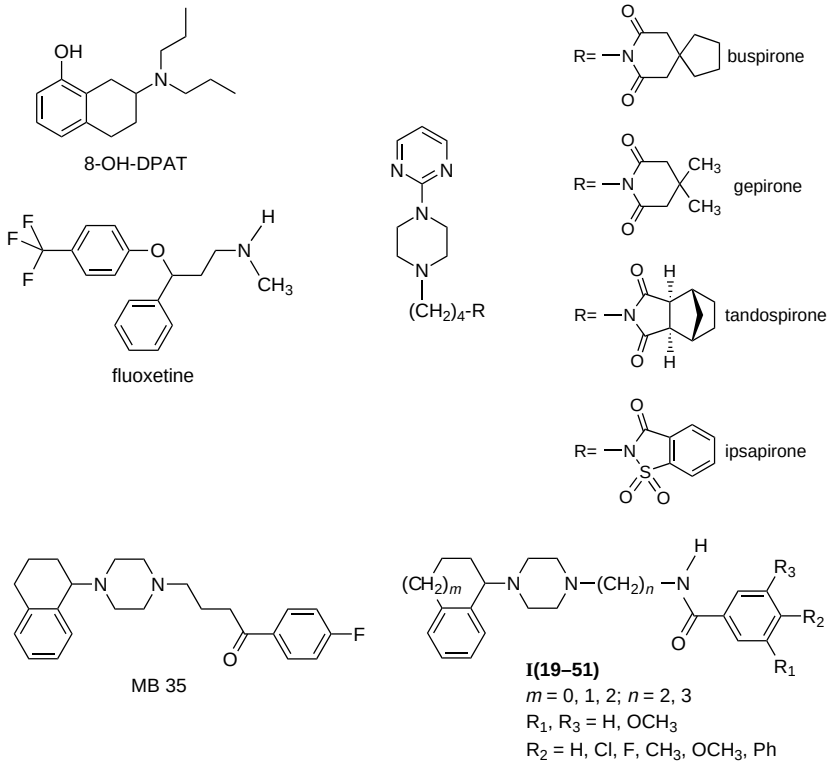
(Benzocycloalkyl)piperazines **I** (**19**−**51**) were prepared by the condensation of substituted benzoyl chlorides (**10**) with 1-(aminoalkyl)-4-(benzocycloalkyl)piperazine (**9a**−**f**) as specified in Scheme 1 (process A).

The reduction of ketones **1a**−**c** with sodium borohydride and subsequent treatment of the corresponding alcohols **2a**−**c** with thionyl chloride gave 1-chlorobenzocycloalkanes (**3a**−**c**). The condensation of ethyl piperazine-1-carboxylate (**4**) with 1-chlorobenzocycloalkanes (**3a**−**c**), followed by saponification and decarboxylation, provided *N*-(benzocycloalkyl)piperazines (**6a**−**c**) via carbamates **5a**−**c**. The treatment of compounds **6a**−**c** with (bromoalkyl)phthalimides (**7**) gave 1-[ω-(2-phthalimido)alkyl]-4-(benzocycloalkyl)piperazines (**8a**−**f**). The removal of phthalimide group[32] by treatment with hydrazine led to the primary amines **9a**−**f**.

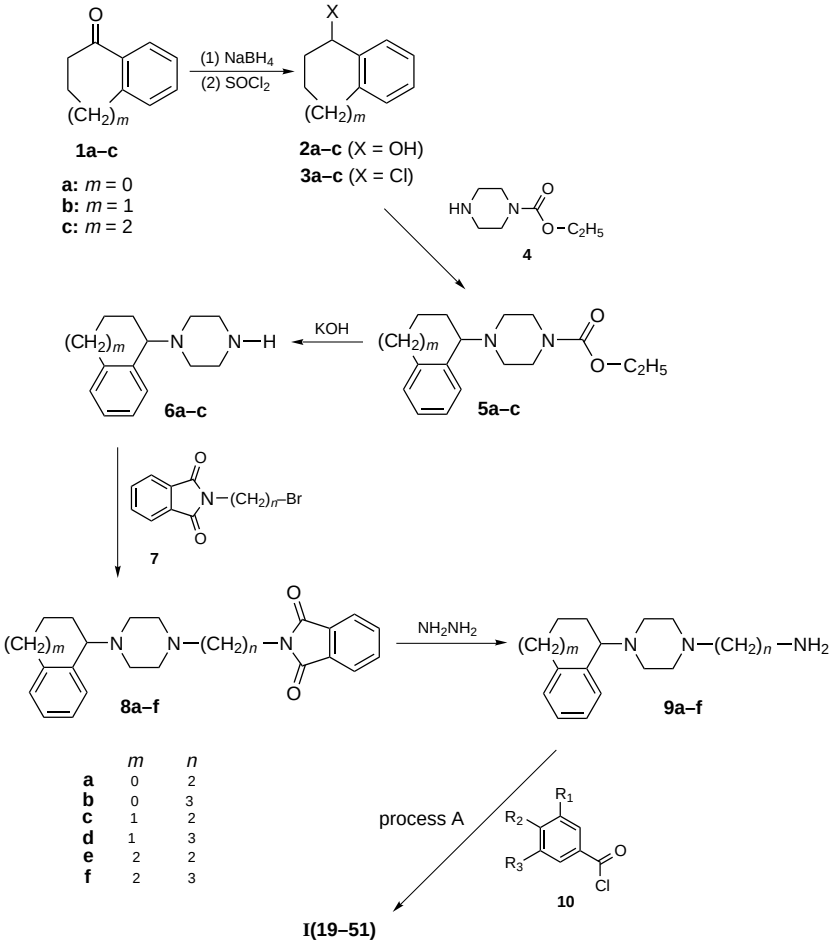
[†] Cooperation Pharmaceutique Française.
[‡] Les Algorythmes.
[⊗] Abstract published in *Advance ACS Abstracts,* February 1, 1997.

S0022-2623(95)00759-X CCC: $14.00

Chart 1

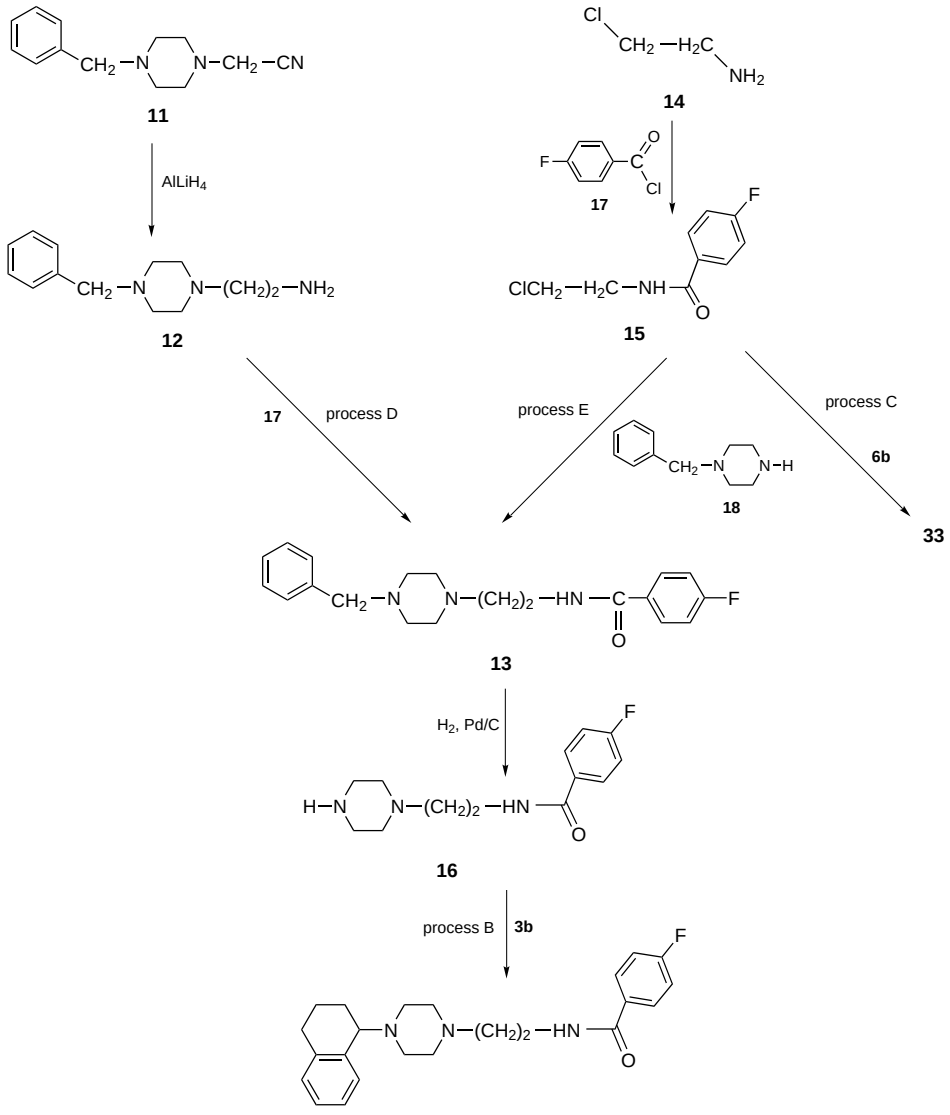


Scheme 1



Other routes were used to prepare the (benzocycloalkyl)piperazines (**19**−**51**). As described in the Scheme 2 for the synthesis of compound **33** ($m = 1$, $n = 2$, $R_1 = R_3 = H$, $R_2 = F$), the condensation of 1-chlorotetralin (**3b**) with 1-[2-(4-fluorobenzamido)-1-ethyl]piperazine (**16**) led to compound **33** (process B).

Scheme 2



1-[2-(4-Fluorobenzamido)-1-ethyl]piperazine (**16**) was prepared by debenzylation of 4-benzyl-1-[2-(4-fluorobenzamido)ethyl]piperazine (**13**), under palladium on active carbon.[33] Piperazine **13** was obtained either by reduction of the nitrile **11** with $AlLiH_4$[34] followed by amidification of the amine **12** with 4-fluorobenzoyl chloride (**17**) (process D) or by amidification of 2-chloroethylamine (**14**) with **17** followed by the reaction of the amide **15** with 1-benzylpiperazine (**18**) (process E).

The condensation of *N*-(2-chloroethyl)-4-fluorobenzamide (**15**) with tetralinylpiperazine (**6b**) afforded compound **33** (process C).

All synthesized compounds are described in Table 5. The yields reported were referring to the process A.

The influence of the stereochemistry on the activity was studied for three tetralin derivatives ($m = 1$), which were the most potent 5-HT_{1A} ligands. The two enantiomers were obtained from the (±)-1-(1,2,3,4-tetrahydronaphthyl)piperazine (**6b**). The levo isomer was obtained by the treatment of the racemic **6b** with 1 equiv of (+)-aspartic acid, the liberation of the crude base, and then, the crystallization of the oxalate. Mother liquors were neutralized with sodium hydroxide, and treated with (+)-tartric acid, and the dextro enantiomer was purified by the crystallization of oxalate salt.

Results and Discussion

Thirty-three 1-(benzocycloalkyl)-4-(benzamidoalkyl)-piperazine derivatives **I** (**19**−**51**) were prepared and evaluated *in vitro*, in a preliminary binding screening, for their affinity for 5-HT_{1A} receptors, and their selectivities were compared to those of three other receptors, 5-HT_2, D_2, and α_1. Products exhibiting an inhibition lower than 30% at 10^{-7} M for all receptors were considered as inactive. Products showing an inhibition more than 30% at 10^{-7} M for one of the four examined receptors in the preliminary binding screening are reported in Table 1.

The products selected on the preliminary binding screening and their enantiomers were tested on an extended binding screening. Affinity constants (K_i) for 11 central receptors have been determined and compared to those for agonists 8-OH-DPAT, buspirone, and MB 35. The results obtained for 5-$HT_{1A,1C,1D,2,3}$,α_1, H_1, $D_{1,2,3}$, and σ receptors are reported in Table 2.

In this work we studied (a) the influence of modifications of the ring size (m), (b) the length of the alkyl side chain (n), (c) the substitutions on the aromatic ring (R_1, R_2, R_3), and (d) the stereochemistry of the benzocycloakyl ring.

Table 1. Preliminary Binding Studies (Percentage of Inhibition at 10^{-7} M)

compd	*m*	*n*	R_1	R_2	R_3	5-HT_{1A}	α_1	5-HT_2	D_2
20	0	2	H	F	H	69 ± 0.8	36 ± 0.3	0	0
23	0	2	H	OCH_3	H	45 ± 1.4	6 ± 2.4	17 ± 3.8	11 ± 1
32	1	2	H	H	H	93 ± 1.3	4 ± 1.2	0	4 ± 1.3
33	1	2	H	F	H	88 ± 0.5	22 ± 2.3	17 ± 5.1	3 ± 0.3
34	1	2	H	Cl	H	86 ± 0.4	23 ± 2.1	6 ± 0.2	29 ± 2
35	1	2	H	CH_3	H	42 ± 0.9	0	6 ± 3.9	5 ± 0.5
37	1	2	H	OCH_3	H	63 ± 2	0	28 ± 2.2	7 ± 1.5
39	1	3	H	H	H	39 ± 1.2	11 ± 0.8	17 ± 1.6	2 ± 0.3
40	1	3	H	F	H	68 ± 1.8	6 ± 0.5	19 ± 1.8	0
45	2	2	H	H	H	51 ± 3.6	0	37 ± 1.8	7 ± 0.7
46	2	2	H	F	H	22 ± 2.9	0	23 ± 0.9	31 ± 0.1
47	2	2	H	CH_3	H	0	0	14 ± 2.1	47 ± 1
49	2	2	H	OCH_3	H	11 ± 1.5	0	10 ± 1	60 ± 0.4
MB 35						37 ± 1	1 ± 0.5	20 ± 0.7	74 ± 0.3

Influence of the Cycloalkyl Size (M). The affinity for 5-HT_{1A} receptors appeared when $m = 0$ (compounds **20** and **23**) was maximal for $m = 1$ (compounds **32**−**35**, **37**, **39**, and **40**), and decreased for $m = 2$ (compounds **45**−**47** and **49**). Compound **45** was the only derivative which showed affinity for the 5-HT_2 receptors. Many substituted benzocycloheptyl derivatives ($m = 2$; compounds **46**, **47**, and **49**) are also bound to dopaminergic D_2 receptors, as MB 35. In this preliminary binding screening, tetralin compounds ($m = 1$) showed the highest affinity for the 5-HT_{1A} receptors.

Influence of the Alkyl Side Chain (*n*). The results reported in Table 1 showed that, except **39** ($n = 3$) and **40** ($n = 3$), the only compounds to be active were the benzamidoethyl ones ($n = 2$; compounds **20**, **23**, **32**−**35**, **37**, **45**−**47**, and **49**). The benzamidopropyl analogs ($n = 3$; compounds **25**−**31**, **41**−**44**, and **51**) did not present any affinity for the selected receptors. These results agreed with those obtained with MB 35 in which distance between the aromatic ring and the nitrogen atom of the piperazine is the same as in the benzamidoethyl analogs.

Influence of the Substituents on the Aromatic Ring (R_1, R_2, and R_3). The highest affinity and selectivity were obtained with the nonsubstituted derivatives ($R_1 = R_2 = R_3 = H$, $m = 1$, $n = 2$, compound **32**; $m = 1$, $n = 3$, compound **39**; $m = n = 2$, compound **45**). The substitution in para position of the aromatic moiety by a halogen, fluorine ($R_1 = R_3 = H$, $R_2 = F$, $m = 0$, $n = 2$, compound **20**; $m = 1$, $n = 2$, compound **33**; $m = 1$, $n = 3$, compound **40**) or chlorine ($R_1 = R_3 = H$, $R_2 = Cl$, $m = 1$, $n = 2$, compound **34**), atoms led to derivatives which presented a good affinity and selectivity for the 5-HT_{1A} receptors. In the tetralyl series ($m = 1$), the substitution in 4-position by a methoxy moiety ($R_1 = R_3 = H$, $R_2 = OCH_3$, $m = 1$, $n = 2$, compound **37**) led to an active compound but had an unfavorable effect on the affinity and selectivity for 5-HT_{1A} receptor. On the other hand, 4-methyl ($R_1 = R_3 = H$, $R_2 = CH_3$, compounds **21**, **28**, **35**, **41**, and **47**), 4-phenyl ($R_1 = R_3 = H$, $R_2 = Ph$; compounds **22**, **29**, **36**, **42**, and **48**), or trimethoxy derivatives ($R_1 = R_2 = R_3 = OCH_3$, compounds **24**, **31**, **38**, **44**, and **50**) were less active or inactive. The tested phthalimide derivatives **17a**−**f** were also inactive.

Influence of the Stereochemistry of the Benzocycloalkyl Ring. The chiral resolution of the high-affinity compounds (**32**, **33**, and **34**) was performed, and enantiomers were tested on an extended binding screening (Table 2). The levo enantiomers **(−)-33** and **(−)-34** showed affinity for 5-HT_{1A} receptors better than that of their dextro isomers and racemates. The chirality of the benzocycloalkyl ring also had a great influence on the selectivity for 5-HT_{1A} receptors. **(+)-33** and **(+)-34** showed poor selectivity vs dopaminergic D_2 and serotoninergic 5-HT receptors. In contrast, levorotatory enantiomers, **(−)-32**, **(−)-33**, and **(−)-34**, presented a high degree of selectivity ($S > 100$) for 5-HT_{1A} receptors compared to all the tested receptors and were more selective than reference compound buspirone. Among levorotatory enantiomers, **(−)-32** possessed the highest affinity and selectivity.

These preliminary structure−activity relationship studies showed that the replacement of the butyrophenone moiety, found in the MB 35 structure, by a benzamidoethyl group had a positive effect on the 5-HT_{1A} selectivity. This structural modulation led to the obtention of new identities among which the compounds **(−)-32**, **(−)-33**, and **(−)-34**, with both greater affinity and higher selectivity for 5-HT_{1A} receptors than MB 35 and buspirone.

Pharmacology

Owing to high 5-HT_{1A} affinity and selectivity, compounds **32**, **33**, **34**, and their enantiomers were selected for further evaluation (i) to determine *in vitro* their postsynaptic agonist/antagonist profile on the adenylate cyclase activity (inhibition cAMP forskolin induced in hippocampus), (ii) to confirm *in vivo* their agonist/antagonist profile, using the lower lip retraction test, and (iii) to compare the potency of racemic compounds and their enantiomers on these tests.

The results of these tests with **32**, **33**, **34**, and their enantiomers **(+)-32**, **(−)-32**, **(+)-33**, **(−)-33**, **(+)-34**, and **(−)-34** are shown in Table 3.

The racemates **32**, **33**, **34**, and the enantiomers **(−)-32**, **(+)-33**, **(−)-33**, **(+)-34**, and **(−)-34** inhibited forskolin-activated adenylate cyclase in rat hippocampi in a concentration-dependent manner, with a similar maximal effect (maximal inhibition = −25%) for the eight compounds. This potency is correlated with the affinity for 5-HT_{1A} receptors. The enantiomers **(−)-32** and **(−)-33** were the most potent compounds with respective IC_{50} = 14 ± 2 and 15 ± 2 nM; their activity was similar to the activity of 8-OH-DPAT. These data suggest that these compounds acted by the stimulation of postsynaptic 5-HT_{1A} receptors as described by Podona et al.[35]

In the lower lip retraction **(−)-32**, **(−)-33**, and **(−)-34** induced a clear lower lip retraction at 2.75, 2.25, and 2.50 mg/kg, respectively. In this test, the levo isomers

Table 2. Extended Binding Screening: Affinities and Selectivity of *N*-(1,2,3,4-Tetrahydronaphthyl)-*N'*-(benzamidoethyl)piperazine Derivatives for Central Receptors (K_i, nM)[a]

compd	**32**	**(−)-32**	**33**	**(+)-33**	**(−)-33**	**34**	**(+)-34**	**(−)-34**	MB 35	DPAT	buspirone
5-HT_{1A}	1.1 ± 0.1 (1)	0.4 ± 0.02 (1)	1.5 ± 0.1 (1)	50 ± 3 (1)	0.5 ± 0.04 (1)	10 ± 0.4 (1)	210 ± 13 (1)	4 ± 0.3 (1)	17 ± 0.3 (1)	0.5 ± 0.04 (1)	7 ± 1 (1)
5-HT_{1C}	1260 ± 190 (1150)	NT	2040 ± 270 (1360)	4050 ± 320 (80)	280 ± 20 (550)	NT	2230 ± 250 (10)	650 ± 100 (160)	NT	14800 ± 1700 (29600)	2270 ± 200 (320)
5-HT_2	710 ± 80 (640)	NT	1180 ± 90 (780)	1300 ± 100 (26)	1380 ± 110 (2760)	1000 ± 34 (100)	3800 ± 680 (18)	2700 ± 260 (670)	66 ± 11 (4)	1100 ± 270 (2200)	1250 ± 150 (180)
5-HT_3	3470 ± 840 (3150)	NT	3470 ± 790 (2310)	NT	NT	NT	NT	NT	3160 ± 1100 (190)	NT	NT
5-HT_{1D}	6920 ± 1030 (6290)	NT	9770 ± 680 (6520)	NT	NT	NT	NT	NT	NT	NT	NT
α_1	150 ± 10 (140)	190 ± 4 (380)	80 ± 2 (50)	710 ± 30 (14)	124 ± 5 (250)	410 ± 41 (40)	8380 ± 340 (40)	450 ± 30 (110)	18 ± 0.8 (1)	9460 ± 380 (18900)	1320 ± 260 (190)
H_1	30 ± 3 (26)	70 ± 14 (130)	140 ± 10 (90)	NT	58 ± 2 (120)	NT	NT	NT	42 ± 3 (3)	NT	NT
D_1	21900 ± 800 (20000)	NT	12000 ± 440 (8000)	2060 ± 120 (40)	3090 ± 150 (6180)	NT	19700 ± 650 (90)	27000 ± 1360 (6780)	1000 ± 18 (59)	87300 ± 8500 (174600)	6100 ± 1040 (870)
D_2	110 ± 10 (100)	130 ± 4 (270)	70 ± 7 (50)	740 ± 80 (15)	70 ± 8 (140)	120 ± 8 (12)	700 ± 70 (3)	480 ± 20 (120)	110 ± 14 (6)	2380 ± 130 (4750)	44 ± 4 (6.3)
D_3	NT	NT	NT	2610 ± 740 (52)	1570 ± 340 (2530)	NT	2200 ± 540 (11)	2110 ± 530 (530)	NT	14600 ± 760 (29200)	660 ± 60 (96)
σ	90 ± 6 (80)	NT	280 ± 10 (180)	190 ± 6 (120)	130 ± 3 (260)	NT	200 ± 6 (0.9)	1250 ± 190 (310)	30 ± 2 (2)	5240 ± 420 (10500)	48 ± 14 (7)

[a] NT = not tested. Selectivity values for 5-HT_{1A} receptors (S = K_i receptor/K_i 5-HT_{1A}) are given in parentheses.

Table 3. Effects of **32**, **33**, **34**, and Their Enantiomers on Electrophysiological and Behavioral Studies

	in vitro tests		
compd	affinity for 5-HT_{1A} receptors K_i (nM)	agonist activity IC_{50} (nM) forskolin[a]	*in vivo* behavioral test LLR[b] msad (mg/kg ip) rats
32	1.1 ± 0.1	36 ± 6	NT
(−)-32	0.4 ± 0.02	14 ± 2	2.75
33	1.5 ± 0.1	52 ± 8.6	NT
(+)-33	50 ± 3	1450 ± 90	NT
(−)-33	0.5 ± 0.04	15 ± 2	2.25
34	10 ± 0.4	75 ± 8	NT
(+)-34	210 ± 13	1500 ± 110	NT
(−)-34	4 ± 0.3	38 ± 3	2.50
MB 35	17 ± 0.3	210 ± 18	>64
8-OH-DPAT	0.5 ± 0.04	14 ± 2	2.20
buspirone	7.1 ± 1	52 ± 7	NT

[a] Inhibition of forskolin-activated adenylate cyclase. [b] Lower lip retraction (msad = minimum significant active dose).

Table 4. Comparison between Literature Data for Reference Compounds and K_i (nM) and S Values for **(−)-32** and **(−)-33**[a]

compd	(−)-32	(−)-33	8-OH DPAT	buspirone
5-HT_{1A} (rat)	0.4 ± 0.02 (1)	0.5 ± 0.04 (1)	0.5 ± 0.1[36] (1)	9.3 ± 0.4[36] (1)
5-HT_{1A} (human)			1.9[37]	15[37]
5-HT_2	NT	1380 ± 110 (2760)	>1000[36] (>2000)	178 ± 23[36] (19)
D_2	130 ± 4 (270)	10 ± 8 (140)	84 ± 6[36] (168)	1000[36] (1.4)
D_1	NT	3090 ± 150 (6180)	1000[36] (> 2000)	1000[36] (>107)
α_1	190 ± 4 (380)	124 ± 5 (250)	>2427[36] (>4850)	>2427[36] (>261)

[a] NT = not tested. Selectivity values for 5-HT_{1A} receptors (S = K_i receptor/K_i 5-HT_{1A}) are given in parentheses.

(−)-32, **(−)-33**, and **(−)-34** are almost as potent as 8-OH-DPAT and acted *in vivo* as agonists on the postsynaptic 5-HT_{1A} receptors.

In comparison with literature data for reference compounds, reported in Table 4, the preferred derivatives **(−)-32** and **(−)-33** showed affinity and selectivity higher than those of buspirone and were comparable to those of 8-OH-DPAT.

As there was no notable difference between affinity for cloned human and rat 5-HT_{1A} receptors as for 8-OH-DPAT and buspirone, it may be suggested that **(−)-32** and **(−)-33** would have a similar affinity for human 5-HT_{1A} receptors and in consequence would present some clinical interest.

Conclusion

The proposed chemical modulation confirmed that the 5-HT_{1A} receptor affinity was supported by the (benzocycloalkyl)piperazinyl moiety. These studies showed that tetralyl (m = 1) compounds were more active than phenylindanyl (m = 0) and benzocycloheptanyl (m = 2) derivatives. The levo enantiomers of selected tetralyl compounds presented the highest affinity and selectivity and were comparable, *in vitro* as well as *in vivo*, to reference compound 8-OH-DPAT. Finally, the replacement of the butyrophenone group found in the MB 35 structure by a benzamidoethyl group permitted us to obtain the expected gain of selectivity in regard to D_2, 5-HT_2, and α_1 receptors. The benzamidopropyl derivatives appeared less potent than ethyl analogs.

Table 5. Physical and Spectrochemical Data of Compounds **I (19−51)**

compd	*m*	*n*	R_1	R_2	R_3	composition[a]	mp (°C)	yield (%)
19	0	2	H	H	H	$C_{22}H_{27}N_3O{\cdot}2HCl$	238	72
20	0	2	H	F	H	$C_{22}H_{26}FN_3O{\cdot}2HCl$	230	71
21	0	2	H	CH_3	H	$C_{23}H_{29}N_3O{\cdot}2HCl$	193	60
22	0	2	H	Ph	H	$C_{28}H_{31}N_3O{\cdot}2HCl$	222	75
23	0	2	H	CH_3O	H	$C_{23}H_{29}N_3O_2{\cdot}2HCl$	172	73
24	0	2	CH_3O	CH_3O	CH_3O	$C_{25}H_{33}N_3O_4{\cdot}2HCl$	207	72
25	0	3	H	H	H	$C_{23}H_{29}N_3O{\cdot}2HCl$	223	75
26	0	3	H	F	H	$C_{23}H_{28}FN_3O{\cdot}2HCl$	198	75
27	0	3	H	Cl	H	$C_{23}H_{28}ClN_3O{\cdot}2HCl$	225	78
28	0	3	H	CH_3	H	$C_{24}H_{31}N_3O{\cdot}2HCl$	228	61
29	0	3	H	Ph	H	$C_{29}H_{33}N_3O{\cdot}2HCl$	235	75
30	0	3	H	CH_3O	H	$C_{24}H_{31}N_3O_2{\cdot}2HCl$	203	72
31	0	3	CH_3O	CH_3O	CH_3O	$C_{26}H_{35}N_3O_4{\cdot}2HCl$	211	62
32[b]	1	2	H	H	H	$C_{23}H_{29}N_3O{\cdot}2HCl$	232	83
33[b]	1	2	H	F	H	$C_{23}H_{28}FN_3O{\cdot}2HCl$	220	83
34[b]	1	2	H	Cl	H	$C_{23}H_{28}ClN_3O{\cdot}2HCl$	225	80
35	1	2	H	CH_3	H	$C_{24}H_{31}N_3O{\cdot}2HCl$	210	71
36	1	2	H	Ph	H	$C_{29}H_{33}N_3O{\cdot}2HCl$	243	70
37	1	2	H	CH_3O	H	$C_{24}H_{31}N_3O_2{\cdot}2HCl$	195	56
38	1	2	CH_3O	CH_3O	CH_3O	$C_{26}H_{35}N_3O_4{\cdot}2HCl$	215	78
39	1	3	H	H	H	$C_{24}H_{31}N_3O{\cdot}2HCl$	193	74
40	1	3	H	F	H	$C_{24}H_{30}FN_3O{\cdot}2HCl$	183	62
41	1	3	H	CH_3	H	$C_{25}H_{33}N_3O{\cdot}2HCl$	222	61
42	1	3	H	Ph	H	$C_{30}H_{35}N_3O{\cdot}2HCl$	208	54
43	1	3	H	CH_3O	H	$C_{25}H_{33}N_3O_2{\cdot}2HCl$	212	61
44	1	3	CH_3O	CH_3O	CH_3O	$C_{27}H_{37}N_3O_4{\cdot}2HCl$	176	59
45	2	2	H	H	H	$C_{24}H_{31}N_3O{\cdot}2HCl$	194	58
46	2	2	H	F	H	$C_{24}H_{30}FN_3O{\cdot}2HCl$	233	62
47	2	2	H	CH_3	H	$C_{25}H_{33}N_3O{\cdot}2HCl$	214	70
48	2	2	H	Ph	H	$C_{30}H_{35}N_3O{\cdot}2HCl$	221	65
49	2	2	H	OCH_3	H	$C_{25}H_{33}N_3O_2{\cdot}2HCl$	212	67
50	2	2	CH_3O	CH_3O	CH_3O	$C_{27}H_{37}N_3O_4{\cdot}2HCl$	194	52
51	2	3	H	F	H	$C_{25}H_{32}FN_3O{\cdot}2HCl$	180	55

[a] Satisfactory elemental analyses (±0.4%) for C, H, N were obtained for all compounds. [b] **(+)-32:** mp 215 °C; yield 82%; $[\alpha]^{22}_D = +60°$ ($c = 0.62$, MeOH). **(−)-32:** mp 215 °C; yield 83%; $[\alpha]^{22}_D = -64°$ ($c = 0.65$, MeOH). **(+)-33:** mp 223 °C; yield 85%; $[\alpha]^{22}_D = +80°$ ($c = 0.73$, MeOH). **(−)-33:** mp 223 °C; yield 79%; $[\alpha]^{22}_D = -77°$ ($c = 0.71$, MeOH). **(+)-34:** mp 232 °C; yield 82%; $[\alpha]^{22}_D = +75°$ ($c = 0.70$, MeOH). **(−)-34:** mp 232 °C; yield 78%; $[\alpha]^{22}_D = -71°$ ($c = 0.66$, MeOH).

Experimental Section

Chemistry. Melting points were determined on a Büchi 535 apparatus and are uncorrected. ^{1}H-NMR spectra of crude bases were recorded on a Hitachi 1500 FT spectrometer (60 MHz). Chemical shifts are given as δ values with reference to Me_4Si as internal standard. Infrared spectra of the bases of final products were performed on a Perkin-Elmer 1500 FT spectrometer. Specific absorptions are given in cm^{-1}. Thin layer chromatography was performed on Merck silica gel 60 plates with fluorescent indicator, and the plates were visualized with UV light (254 nm). Flash chromatography was conducted on Merck Kieselgel 60 (0.040−0.063). Elemental analyses were carried out by the Microanalysis Laboratory of the Faculty of Pharmacy in Chatenay-Malabry, France, and agreed to within ±0.4% of calculated values. The optical purity of enantiomers was determined by an HPLC method using a chiral column SCI ULTRON (ES-OVM 4.6 × 150) performed on a L 4500 Hitachi spectrometer. Optical rotation (α) of the pure enantiomers was measured by an AA10 optical activity polarimeter.

1-[2-(4-Fluorobenzamido)-1-ethyl]-4-(1,2,3,4-tetrahydronaphth-1-yl)piperazine Dihydrochloride (33). Process A. A mixture of 1-(2-amino-1-ethyl)-4-(1,2,3,4-tetrahydronaphth-1-yl)piperazine (**9c**) (2.59 g, 10 mmol), triethylamine (2 mL), and 50 mL of chloroform was cooled to 5 °C. 4-Fluorobenzoyl chloride (**17**) (1.58 g, 10 mmol) in 20 mL of chloroform was added dropwise to the mixture at $t < 10$ °C. Then the reaction mixture was stirred for 4 h. The solvent was evaporated to dryness, the residue was taken up with water, and extracted with dichloromethane, and the organic phase was washed with 2 M NaOH. The product was purified by chromatography on a silica column (eluent, 0.5% Et_3N/ethyl acetate) to yield 3.16 g (83%) of a pure product **33**. Compounds **I** (**19**−**51**) were prepared according this process.

Process B. A mixture of 1-[2-(4-fluorobenzamido)ethyl]-piperazine (**16**) (4 g, 15.9 mmol), 1-chlorotetralin (**3b**) (2.65 g, 15.9 mmol), potassium carbonate (5.55 g, 40 mmol), and sodium iodide (0.5 g, 3.3 mmol) in 150 mL of methyl ethyl ketone was refluxed for 24 h. The solution was then evaporated to dryness, and the residue was taken up with water and extracted with ethyl acetate. The organic layer was separated, dried, and evaporated, and the residue was purified by chromatography on a silica column (eluent, 0.5% Et_3N/ethyl acetate) to yield 3.3 g (54%) of pure product **33**.

Process C. A mixture of 1-(1,2,3,4-tetrahydronaphth-1-yl)-piperazine (**6b**) (5.4 g, 25 mmol), *N*-(2-chloroethyl)-4-fluorobenzamide (**15**) (5.04 g, 25 mmol), and 8 mL of triethylamine in 100 mL of DMF was heated at 60 °C for 48 h. After cooling, the reaction mixture was poured all at once into 200 mL of water and then extracted with ethyl acetate. The organic phase was dried and evaporated under vacuum. The residue was purified by chromatography on a silica column (eluent, 0.5% Et_3N/ethyl acetate) to yield 3g (31%) of a pure product **33**.

Preparation of the Dihydrochloride. The base dissolved in alcohol was added with alcoholic solution of hydrogen chloride and the salt crystallized out. Physicochemical data are shown in Table 5. Spectral data are available as Supporting Information.

Ethyl 4-(Benzocycloalkyl)piperazine-1-carboxylate (5a−c). A mixture of 1-chlorobenzocycloalkane (**3a**−**c**) (0.65 mol), ethyl piperazine-1-carboxylate (**4**) (124.8 g, 0.79 mol), potassium carbonate (197.34 g, 1.43 mol), and sodium iodide (10 g, 0.06 mol) in 1 L of acetonitrile was refluxed for 24 h. After cooling, the mixture was filtered and the solvent was evaporated off. The residual oil was taken up with ice−water, and the product was extracted three times with ethyl acetate. A solution of hydrogen chloride was then added. The hydrochloride formed was filtered off. The base was displaced from its salt with sodium carbonate in a dichloromethane/water mixture. The organic layer was separated, dried, and evaporated under vacuum to give an oil. **5a**: $m = 0$; 70% yield; ^{1}H

Table 6. Physicochemical Properties of Compounds **8a**−**f**

compd	*m*	*n*	mp (°C) (salt, 2HCl)	yield (%)	NMR ($CDCl_3$) (base) δ
8a	0	2	252	72	2.1 (q, 2H, *J* = 7 Hz), 2.4−3 (m, 12H), 3.8 (t, 2H, *J* = 7.3 Hz), 4.3 (t, 1H, *J* = 7 Hz), 7.2−7.8 (m, 8H)
8b	0	3	243	74	1.65−2.1 (m, 4H), 2.4−2.9 (m, 12H), 3.8 (t, 2H, *J* = 7.3 Hz), 4.3 (t, 1H, *J* = 7 Hz), 7.2−7.8 (m, 8H)
8c[a]	1	2	231	72	1.6−1.9 (m, 4H), 2.3−2.8 (m, 12H), 3.75 (t, 1H, *J* = 7 Hz), 3.85 (t, 2H, *J* = 7.5 Hz), 7-7.9 (m, 8H)
8d	1	3	169	68	1.6−2.1 (m, 6H), 2.4−2.9 (m, 12H), 3.75 (t, 1H, *J* = 7 Hz), 3.85 (t, 2H, *J* = 7.5 Hz), 7−7.9 (m, 8H)
8e	2	2	249	65	1.5−2.15 (m, 6H), 2.25−2.8 (m, 12H), 3.1 (t, 1H, *J* = 7 Hz), 3.8 (t, 2H, *J* = 7.3 Hz), 7−7.8 (m, 8H)
8f	2	3	254	69	1.45−2.1 (m, 8H), 2.3−2.85 (m, 12H), 3.1 (t, 1H, *J* = 7 Hz), 3.75 (t, 2H, *J* = 7.3 Hz), 7−7.9 (m, 8H)

[a] **(+)-8c**: mp 223 °C; $[\alpha]^{25}_D = +96.3°$ (*c* = 2.49, MeOH). **(−)-8c**: mp 222 °C; $[\alpha]^{25}_D = -104.5°$ (*c* = 2.58, MeOH).

NMR ($CDCl_3$) δ 1.25 (t, 3H, *J* = 7 Hz), 2.1 (q, 2H, *J* = 7 Hz), 2.3−2.9 (m, 6H), 3.5 (t, 4H, *J* = 6 Hz), 4.15 (q, 2H, *J* = 7 Hz), 4.35 (t, 1H, *J* = 7 Hz), 7−7.7 (m, 4H). **5b**: *m* = 1; 63% yield; ^{1}H NMR ($CDCl_3$) δ 1.25 (t, 3H, *J* = 7 Hz), 1.6−2.1 (m, 4H), 2.3−2.9 (m, 6H), 3.5 (t, 4H, *J* = 6 Hz), 3.8 (t, 1H, *J* = 7 Hz), 4.15 (q, 2H, *J* = 7 Hz), 7−7.75 (m, 4H). **5c**: *m* = 2; 61% yield; ^{1}H NMR ($CDCl_3$) δ 1.25 (t, 3H, *J* = 7 Hz), 1.4−2 (m, 6H), 2.4−2.9 (m, 6H), 3.15 (t, 1H, *J* = 7 Hz), 3.45 (t, 4H, *J* = 6 Hz), 4.15 (q, 2H, *J* = 7 Hz), 7−7.2 (m, 4H).

(±) 1-(Benzocycloalkyl)piperazines (6a−c). Potassium hydroxide (300 g, 5.36 mol) was slowly added to a solution of ethyl 4-(benzocycloalkyl)piperazine-1-carboxylate (**5a**−**c**) (0.46 mol), water (100 mL), and methanol (400 mL). The reaction mixture was refluxed. The reaction was monitored by thin layer chromatography. After the starting material had disappeared, the mixture was cooled, filtered, and extracted with dichloromethane. The organic layer was separated, dried, and evaporated. The residual oil was taken up with ethanol, and oxalic acid (39.33 g, 0.44 mol) dissolved in ethanol was added. The oxalate formed was filtered off, and the base was displaced from its salt with sodium carbonate in a dichloromethane/water mixture. The organic layer was dried, and the solvent was evaporated under vacuum to give an oil. **6a**: *m* = 0; 83% yield; ^{1}H NMR ($CDCl_3$) δ 2.1 (t, 2H, *J* = 7 Hz), 2.4−2.85 (m, 7H), 2.9 (t, 4H, *J* = 6 Hz), 4.3 (t, 1H, *J* = 7 Hz), 7−7.7 (m, 4H). **6b**: *m* = 1; 84% yield; ^{1}H NMR ($CDCl_3$) δ 1.5−2.1 (m, 4H), 2 (s, NH), 2.4−2.8 (m, 6H), 2.9 (t, 4H, *J* = 6 Hz), 3,75 (t, 1H, *J* = 7 Hz), 7−7.8 (m, 4H). **6c**: *m* = 2; 70% yield; ^{1}H NMR ($CDCl_3$) δ 1.3−2.1 (m, 6H), 2.3−2.75 (m, 6H), 2.9 (t, 4H, *J* = 6 Hz), 3.2 (t, 1H, *J* = 7 Hz), 3.9 (s, NH), 7.1 (m, 4H).

(−)-1-(1,2,3,4-Tetrahydronaphth-1-yl)piperazine ((−)-6b). (+)-L-Aspartic acid (3.6 g, 27 mmol) was added to a solution of racemic **6b** (7.4 g, 34 mmol) in 70 mL of ethanol (95%). The mixture was refluxed for a few minutes and then left to stand at room temperature for 3 or 4 h. The precipitate formed was filtered off and dried to give 4.67 g (13.3 mmol) of aspartate (39% based on the **6b**). The solid obtained was decomposed with 150 mL of 3 M NaOH. The aqueous phase was extracted with diethyl ether. The organic layer was dried and evaporated under vacuum to give an oil (1.92 g, 8.8 mmol) of impure **(−)-6b** (26% of the initial **6b**): $[\alpha]^{25}_D = -114°$ (*c* = 1.64; 95% EtOH); enantiomeric excess (ee) 41%.

A solution of the impure (−)-**6b** (1.92 g, 8.8 mmol) in 80 mL of ethanol (95%) was treated with oxalic acid dihydrate (1.2 g, 9.5 mmol). The oxalate obtained was filtered and dried to give 2.1 g (6.8 mmol) of (−)-oxalate salt: 76% yield; $[\alpha]^{25}_D = -32°$ (*c* = 1.64; 95% H_2O); mp 202−203 °C; ee = 100%. The free amine was obtained by decomposing the oxalate with 3 M NaOH.

(+)-1-(1,2,3,4-Tetrahydronaphth-1-yl)piperazine ((+)-6b). Mother liquors of aspartate were evaporated to dryness (7.14 g), and the residue was treated with 3 M NaOH. The product was extracted with diethyl ether. The organic layer was dried and evaporated to give an oil (5.02 g, 23 mmol) (69%) of impure **(+)-6b**: $[\alpha]^{25}_D = +50°$ (*c* = 1.38; 95% EtOH); ee = 41%.

A solution of this impure **(+)-6b** (5 g, 23 mmol) in 200 mL of ethanol (95%) was treated with (+)-tartaric acid (3.47 g, 23 mmol). The mixture was refluxed for a few minutes and then left to stand at room temperature for about 3 h. The precipitated tartrate was filtered off and dried (5.5 g, 15 mmol; 65% yield). The tartrate was displaced with 3 M NaOH. The base was extracted with diethyl ether. A chemical treatment led to an oil (3.05 g, 14 mmol) of **(+)-6b**: $[\alpha]^{25}_D = +99°$ (*c* = 1.62; 95% EtOH); ee = 81%.

A solution of this impure **(+)-6b** (3 g, 14 mmol) in 120 mL of ethanol (95%) was treated with oxalic acid dihydrate (1.76 g, 14 mmol). The oxalate obtained was filtered off and dried to give 3.25 g (76%): $[\alpha]^{25}_D = +29°$ (*c* = 1.52; H_2O); ee = 97%. The free **(+)-6b** was obtained by decomposing the oxalate with 3 N NaOH.

1-(2-Phthalimido-1-alkyl)-4-(benzocycloalkyl)piperazine (8a−f). A mixture of 1-(benzocycloalkyl)piperazine (**6a**−**c**) (50 mmol), (bromoalkyl)phthalimide (**7**) (65 mmol), potassium carbonate (17.25 g, 125 mmol), and sodium iodide (1 g, 6 mmol) in 200 mL of acetonitrile was refluxed for 24 h. The solvent was evaporated off to dryness. The residue was taken up with water and extracted with dichloromethane. The organic layer was separated, dried, and evaporated, and the residue was purified by chromatography on a silica column (eluent, 35% ethyl acetate/cyclohexane). Physicochemical properties are reported in Table 6.

1-(Aminoalkyl)-4-(benzocycloalkyl)piperazine (9a−f). A mixture of 1-(2-phthalimido-1-alkyl)-4-(benzocycloalkyl)-piperazine (**8a**−**f**) (29 mmol) and hydrazine hydrate (3.4 g, 68 mmol) in 200 mL of methanol was stirred at room temperature. The reaction was monitored by thin layer chromatography. After the starting material had disappeared, the solvent was evaporated under vacuum, 150 mL of 2 M HCl was added, and the mixture was stirred for 2 h. The solid formed was filtered off, the filtrate was neutralized with sodium carbonate, and the product was extracted with ethyl acetate to give a thick oil. **9a**: *m* = 0; *n* = 2; 70% yield; ^{1}H NMR ($CDCl_3$) δ 2.1 (q, 2H, *J* = 7 Hz), 2.3−2.9 (m, 16H), 4.4 (t, 1H, *J* = 7 Hz), 7.1−7.9 (m, 4H). **9b**: *m* = 0; *n* = 3; 80% yield; ^{1}H NMR ($CDCl_3$) δ 1.6−2.2 (m, 4H), 2.3−2.9 (m, 16H), 4.4 (t, 1H, *J* = 7 Hz), 7.1−7.85 (m, 4H). **9c**: *m* = 1; *n* = 2; 81% yield; ^{1}H NMR ($CDCl_3$) δ 1.6−2 (m, 4H), 2.1 (s, NH_2), 2.4−3 (m, 14H), 3.8 (t, 1H, *J* = 7 Hz), 7−7.85 (m, 4H). **9d**: *m* = 1; *n* = 3; 78% yield; ^{1}H NMR ($CDCl_3$) δ 1.6−2 (m, 6H), 2.2−3 (m, 16H), 3.8 (t, 1H, *J* = 7 Hz), 7−7.8 (m, 4H). **9e**: *m* = 2; *n* = 2; 75% yield; ^{1}H NMR ($CDCl_3$) δ 1.4−2.1 (m, 6H), 2.2−3 (m, 16H), 3.15 (t, 1H, *J* = 7 Hz), 6.9−7.25 (m, 4H). **9f**: *m* = 2; *n* = 3; 69% yield; ^{1}H NMR (CDCl3) δ 1.4−2.1 (m, 8H), 2.2−3 (m, 16H), 3.15 (t, 1H, *J* = 7 Hz), 6.95−7.2 (m, 4H).

1-Hydroxybenzocycloalkanes (2a−c). Sodium borohydride (2.32 g, 61 mmol) was added in portions with stirring at 15 °C to a solution of **1a**−**c** (183 mmol) in methanol (500 mL). The mixture was stirred at room temperature for 2 h and then evaporated. The resulting oil was treated with water and diethyl ether, and the organic phase was separated, washed with water and 0.1 M HCl, dried, and evaporated to dryness. **2a**: *m* = 0; 88% yield; ^{1}H NMR ($CDCl_3$) δ 2.1 (q, 2H, *J* = 7 Hz), 2.25 (s, 1H, OH), 2.9 (t, 2H, *J* = 7 Hz), 5.2 (t, 1H, *J* = 7 Hz), 7.25 (m, 4H). **2b**: *m* = 1; 97% yield; ^{1}H NMR ($CDCl_3$) δ 1.6 −2.3 (m, 5H), 2.8 (t, 2H, *J* = 7 Hz), 4.95 (t, 1H, *J* = 7 Hz), 7−7.6 (m, 4H).; **2c**: *m* = 2; mp 102 °C; 85% yield; ^{1}H NMR ($CDCl_3$) δ 1.4 −2.2 (m, 7H), 2.8 (t, 2H, *J* = 7 Hz), 4.75 (t, 1H, *J* = 7 Hz), 7−7.4 (m, 4H)

1-Chlorobenzocycloalkanes (3a−c). Thionyl chloride (26 mL, 0.35 mol) was added at 15 °C to a solution of **2a**−**c** (0.238 mol) in toluene (340 mL). The mixture was stirred at room temperature for 30 min and then heated to 55 °C for 1 h. The mixture was cooled, washed twice with ice−water, dried, and evaporated to give quantitatively **3a**−**c** as an oil, which was used without further purification in the next step. **3a**: *m* =

Table 7. Binding Conditions

receptor	ligands concentration	structures	reference compounds	K_i (nM)	prot/mL	incubation conditions	nonspecific
α_1	[^{3}H]prazozin 0.5 nM	frontal cortex calf	WB4101	0.6	0.8 mg	40 min, 25 °C	prazozine
D_1	[^{3}H]SCH23390 0.5 nM	striatum bovine	fluanxol	18	0.8 mg	60 min, 25 °C	(+)butaclamol, 10^{-5} M
D_2	[^{3}H]raclopride 1.2 nM	striatum bovine	pimozide	0.6	0.8 mg	60 min, 25 °C	spiperone, 10^{-5} M
D_3	[^{3}H]spiperone 1.2 nM	cortex	haloperidol	115	0.5 mg	60 min, 25 °C	haloperidol, 10^{-5} M
5-HT_{1A}	[^{3}H]-8-OH-DPAT 0.5 nM	hippocampus + frontal cortex bovine	buspirone	8.6	0.5 mg	40 min, 23 °C	buspirone
5-HT_{1C}	[^{3}H]mesulergine 1.2 nM	choroïd Plexus pig	mianserin	3.8	0.2 mg	60 min, 25 °C	mianserin
5-HT_{1D}	[^{3}H]-5-OH-tryptamine 2 nM	striatum + frontal Cortex pig	butotenin	5.8	0.8 mg	30 min, 25 °C	5-HT, 10^{-5} M
5-HT_2	[^{3}H]ketanserin 0.8 nM	frontal cortex bovine	spiperone	5.3	0.6 mg	30 min, 37 °C	ketanserin
5-HT_3	[^{3}H]BRL43694 1 nM	NG cells 108-15	ICS 205930	33	10^{-6} cells	60 min, 25 °C	ICS 205930
H_1	[^{3}H]pyrilamine 1 nM	cortex rat	tripolidine	12	0.5 mg	40 min, 25 °C	tripolidine, 10^{-6} M
σ	[^{3}H]DTG 4 nM	hippocampus rat	haloperidol	38	0.6 mg	120 min, 23 °C	haloperidol

0; ^{1}H NMR (CDCl3) δ 2.35 (q, 2H, J = 7 Hz), 2.95 (t, 2H, J = 7 Hz), 5.4 (t, 1H, J = 7 Hz), 7.1−7.5 (m, 4H). **3b**: m = 1; ^{1}H NMR (CDCl3) δ 1.7−2.5 (m, 4H), 2.8 (t, 2H, J = 7 Hz), 5.3 (t, 1H, J = 7 Hz), 7−7.3 (m, 4H). **3c**: m = 2; ^{1}H NMR (CDCl3) δ 1.4 −2.6 (m, 6H), 2.8 (t, 2H, J = 7 Hz), 5.2 (t, 1H, J = 7 Hz), 7.2 (m, 4H).

1-Benzyl-4-(cyanomethyl)piperazine (11). Bromoacetonitrile (14.56 g, 0.12 mol) in 10 mL of DMF was added dropwise to a mixture of 4-benzylpiperazine (17.6 g, 0.1 mol) and potassium carbonate (17.6 g, 0.127 mol) in 100 mL of DMF. The temperature rose to 35 °C. After the mixture was stirred for 24 h at room temperature, 100 mL of water were added, and the mixture was extracted twice with ethyl acetate, the organic phase was washed twice with water, dried, and evaporated to give an oil (85% yield): ^{1}H NMR ($CDCl_3$) δ 2.55 (m, 8H), 3.5 (s, 4H), 7.3 (m, 5H).

***N*-(2-Amino-1-ethyl)-4-benzylpiperazine (12).** 1-Benzyl-4-(cyanomethyl)piperazine (**11**) (10.5 g, 0.049 mol) in 10 mL of THF was added dropwise, at 10 °C, to a slurry of $LiAlH_4$ (2.6 g, 0.068 mol) in 100 mL of THF, under a nitrogen atmosphere. The mixture was then refluxed for 6 h, cooled to 0 °C, and hydrolyzed by the dropwise addition of 3 mL of ice−water and then 3 mL of 15% NaOH. The solids were filtered and rinsed with diethyl ether. The solution was dried, filtered, and evaporated to yield 8.6 g (80%): ^{1}H NMR ($CDCl_3$) δ 1.9 (s, NH_2), 2.5 (m, 10H), 2.7 (t, 2H, J = 7 Hz), 3.5 (s, 2H), 7.3 (m, 5H).

***N*-(2-Chloroethyl)-4-fluorobenzamide (15).** 4-Fluorobenzoyl chloride (**17**) (33.05 g, 0.21 mol) dissolved in 50 mL of dichloromethane was added dropwise to an aqueous solution (100 mL) of chloroethylamine hydrochloride (**14**) (26.6 g, 0.23 mol) and potassium carbonate (37.4 g, 0.27 mol). After being stirred for 24 h, the reaction mixture was extracted with dichloromethane. The organic layer was dried and then concentrated under vacuum to give 40 g (83.5%) of a solid: mp 108 °C; ^{1}H NMR ($CDCl_3$) δ 3.65−3.85 (m, 4H), 6.75 (NH), 6.9−7.9 (m, 4H).

4-Benzyl-1-[2-(4-fluorobenzamido)-1-ethyl]piperazine Dihydrochloride (13). Process D. This procedure is the same as the process A. Initial products were **12** and **17** (yield, 83%).

Process E. Compound **15** (20.15 g, 0.1 mol) in solution in 50 mL of DMF was added dropwise to a mixture of 1-benzylpiperazine (**18**) (35.2 g, 0.2 mol) and sodium iodide (1 g, 6.6 mmol) in 150 mL of DMF. The reaction mixture was stirred for 4 h at room temperature and then for 2 h at 65 °C. After the mixture was cooled, water was added and the mixture was extracted with ethyl acetate. The organic layer was washed several times with water, dried, and then evaporated to give 29 g of crude base (85% yield). This base was dissolved in ethanol, a solution of hydrogen chloride in ethanol was then added, and the dihydrochloride crystallized out: mp 201 °C; ^{1}H NMR (base) δ 2.4−2.7 (m, 10H), 3.45 (s, 2H), 3.55 (q, 2H, J = 6 Hz), 6.85 (NH), 7.2−7.8 (m, 9H).

1-[2-(4-Fluorobenzamido)-1-ethyl]piperazine (16). Compound **13** (25 g, 0.06 mol) was dissolved in a mixture of 100 mL of water and 100 mL of ethanol. Then, 3 g of 10% Pd/C was added. Hydrogenolysis was carried out at room temperature until the absorption of the theoretical hydrogen volume. The reaction mixture was filtered, and the filtrate was neutralized with 2 M NaOH and evaporated to dryness. The residue was taken up with dichloromethane and filtered. The filtrate was dried, filtered, and concentrated under vacuum to give a pasty product: yield 91.3%; ^{1}H NMR ($CDCl_3$) δ 2.25 (NH amine), 2.3−2.65 (m, 6H), 2.75−3 (m, 4H), 3.5 (q, 2H, J = 6 Hz), 7.05 (NH amide), 7.2−7.9 (m, 4H).

Biology: Binding Experiments. Receptor preliminary assays were carried out using methods described in the literature. Three concentrations were tested: 10^{-5}, 10^{-7}, and 10^{-9} M. The serotoninergic 5-HT_{1A} and 5-HT_2, the dopaminergic D_2, and the adrenergic α_1 receptors were examined in the preliminary assays. 5-HT_{1A} assays used rat hippocampal membranes and [^{3}H]-8-OH-DPAT,[38] 5-HT_2 assays used bovine frontal cortex preparations and [^{3}H]ketanserin,[39] D2 assays used bovine striatal preparations and [^{3}H]YM09151-2,[40] and α_1 assays used calf frontal cortex preparations and [^{3}H]-prazosin.[41] Results were expressed as inhibition percentage compared to results without drug.

The selected compounds were examined on a larger screening. Operating conditions and results obtained with reference compounds are summarized in Table 7.

Only the results of the compounds for which inhibition was superior to 30% at 10^{-7} M for one receptor are reported in Table 1.

Adenylate Cyclase Activity. Hippocampi of Wistar rats were dissected immediately after death, and the tissues were homogeneizated and centrifuged. Proteins were dosed by the Lowry's protocol. The enzymatic activity was measured from conversion of [^{32}P]-α -ATP into [^{32}P]cAMP at the end of a 20 min incubation at 30 °C, in the presence of forskolin, as described by Salomon[42] and Coll. Concentration−effect curves were analyzed using a nonlinear regression computer program and the results expressed as percentage of maximal inhibition and IC_{50} values.

Lower Lip Retraction Test in Rats.[43] Rats were administered ip with the tested compounds and immediately afterward were placed individually in transparent plexiglass cages (20 × 10 × 10 cm). Lower lip retraction was scored every 15 min for 3 h after injection according to the following scale: 0 = lower incisors not visible, 1 = lower incisors partly visible, 2 = lower incisors completely visible. Scores were cumulated per rat. Six rats were used per group. All quantitative data were analyzed for their overall statistical significance using the Wilcoxon test.

Acknowledgment. We thank Carole Lecinse for linguistic advice.

Supporting Information Available: Spectrochemical data of compounds **I** (**19**−**51**) (2 pages). Ordering information is given on any current masthead page.

References

(1) Johnston, A. L.; File, S. E. 5-HT and Anxiety: Promises and Pitfalls. *Pharmacol. Biochem. Behav.* **1986**, *24*, 1467−1470.

(2) Eison, M. S. Use of Animal Model: toward Anxioselective Drugs. *Psychopathology* **1984**, *17*, 37−44.
(3) Peroutka, S. J.; Snyder, S. H. [^{3}H] Mianserin: Differential Labelling of Serotonin$_2$ and Histamin$_1$ Receptors in Rat Brain. J. *Pharmacol. Exp. Ther.* **1981**, *216*, 142−148.
(4) Fuller, R. W. Minireview Uptake Inhibitors Increase Extracellular Serotonin Concentration Measured by Brain Microdialysis. *Life Sci.* **1994**, *55*, 163−167.
(5) Saxena, P. R.; Ferrari, M. D. 5-HT$_1$-like Receptor Agonists and the Pathophysiology of Migraine. *Trends Pharmacol. Sci.* **1989**, *10*, 200−204.
(6) Clarke, D. E.; Craig, D. A.; Fozard, J. R. The 5-HT$_4$ Receptor: Naughty, but Nice. *Trends Pharmacol. Sci.* **1989**, *10*, 385−386.
(7) Hoyer, D.; Clarke, D. E.; Fozard, J. R.; Hartig, P. R.; Martin, G. R.; Mylecharane, E. J.; Saxena, P. R.; Humphery, P. P. A. International Union of Pharmacology Classification of Receptors for 5-Hydroxytryptamine (Serotonin). *Pharmacol. Rev.* **1994**, *46* (2), 157−203.
(8) Thielen, R. J.; Frazer, A. Effects of Novel 5-HT$_{1A}$ Receptor Antagonists on Measures of Post-synaptic 5-HT$_{1A}$ Receptor Activation *in vivo*. *Life Sci.* **1995**, *56*, PL 163−168.
(9) Fuller, R. W. Serotonin Receptors and Neuroendocrine Responses. *Neuropsychopharmacology* **1990**, *3*, 495−502.
(10) Sprouse, J. S.; Aghajanian, G. K. Electrophysiological Responses of Serotoninergic Dorsal Raphe Neurons to 5-HT$_{1A}$ and 5-HT1B Agonists. *Synapse* **1987**, *1*, 3−9.
(11) Tricklebank, M. D. The Behavioural Response to 5-HT Receptor Agonists and Subtypes of the Central 5-HT Receptor. *Trends Pharmacol. Sci.* **1985**, *6*, 403−407.
(12) Middbennis, D. N.; Fozard, J. R. 8-Hydroxy-2-(di-n-propylamino)-tetralin. Discriminates between Subtypes of the 5-HT$_1$ Recognition Site. *Eur. J. Pharmacol.* **1983**, *90*, 151−153.
(13) Glennon, R. A. Concepts for Design of 5-HT$_{1A}$,Serotonin Agonists and Antagonists. *Drug Dev. Res.* **1992**, *26*, 251−274.
(14) Martier, P.; Tissier, M. H.; Adrien, J.; Puech, A. J. Antidepressant-like Effects of Buspirone Mediated by the 5-HT$_{1A}$ Postsynaptic Receptors in the Learned Helplessness Paradigm. *Life Sci.* **1991**, *48* (26), 2505−2511.
(15) Chojnackawojcik, E.; Tatarczynska, E.; Golembiowska, K.; Przegalinski, E. Involvement of 5-HT$_{1A}$ Receptors in the Antidepressant-like Activity of Gepirone in the Forced Swimming Test in Rats. *Neuropharmacology* **1991**, *30* (7), 711.
(16) Kataoka, Y.; Shibata, K.; Miyazaki, A.; Inoue, Y.; Koizumi, S.; Ueki, S.; Niwa, M. Involvement of the Dorsal Hippocampus in Mediation of the Antianxiety Action of Tandospirone, a 5-Hydroxytryptamine 1A Agonistic Anxiolytic. *Neuropharmacology* **1991**, *30* (5), 475−480.
(17) Erandez-Guasti, A.; Lopez-Rubalcava, C. Evidence for the Involvement of the 5-HT$_{1A}$ Receptors in the Anxiolytic Action of Indorenate and Ipsapirone. *Psychopharmacol.* **1990**, *101*, 354−358.
(18) Iversen, S. D. 5-HT and Anxiety. *Neuropharmacology* **1984**, *23*, 1553−1560.
(19) Barrett, J. E.; Vanover, K. E. 5-HT Receptors as Targets for the Development of Novel Anxiolytic Drugs: Models, Mechanisms and Future Directions. *Psychopharmacology* **1993**, *112*, 1−12.
(20) Hjorth, S. Serotonin 5-HT$_{1A}$ Autoreceptor Blockade Potentiates the Ability of the 5-HT Reuptake Inhibitor Citalopram to Increase Nerve Terminal Output of 5-HT *in vivo*: a Microdialysis Study. *J. Neurochem.* **1993**, *60*, 776−779.
(21) Lucot, J. B.; Crampton, G. H. 8-OH-DPAT Suppresses Vomiting in the Cat Elicited by Motion, Cisplatin or Xylazine. *Pharmacol. Biochem. Behav.* **1989**, *33*, 627−631.
(22) Lucot, J. B. Antiemetic Effects of Flesinoxan in Cats: Comparisons with 8-Hydroxy-2-(di-n-propylamino)tetralin. *Eur. J. Pharmacol.* **1994**, *253*, 53−60.
(23) Bowen, D. M.; Francis, P. T.; Procter, A. W.; Halliwell, J. V.; Mann, D. M. A.; Neary, M. D. Treatment Strategy for the Corticocortical Neuron Pathology of Alzheimer's Disease. *Ann. Neurol.* **1992**, *32*, 112.
(24) Abdul, M.; Anezinis, P. E.; Logothetis, C. J.; Hoosein, N. M. Growth Inhibition of Human Prostatic Carcinoma Cell Lines by Serotonin Antagonists. *Anticancer Res.* **1994**, *14*, 1215−1220.
(25) Lavielle, G.; Laubie, M.; Colpaert, F. Nouveaux Dérivés de la Pipéridine, de la Tétrahydropyridine et de la Pyrrolidine, leur Procédé de Préparation et les Compositions Pharmaceutiques qui les Contiennent. EP 466 585, 1991.
(26) Lavielle, G.; Laubie, M.; Colpaert, F. Nouveaux Dérivés de Napht-1-yl pipérazines, leur Procédé de Préparation et les Compositions Pharmaceutiques qui les Contiennent. EP 434 561, 1990.
(27) Eison, M. S. The New Generation of Serotoninergic Anxiolytics: Possible Clinical Roles. *Psychopathology* **1989**, *22*, 1, 13−20.
(28) Feighner, J. P.; Boyer, W. F. Serotonin-1A Anxiolytics: an Overview. *Psychopathology* **1989**, *22*, 1, 21−26.
(29) Tollefson, G. D. Serotonin and Alcohol: Interrelationships. *Psychopathology* **1989**, *22*, 1, 37−48.
(30) Kostowski, W.; Dyr, W. Effects of 5-HT$_{1A}$ Receptor Agonists on Ethanol Preference in the Rat. *Alcohol* **1992**, *9* (4), 283−286.
(31) Buzas, A.; Ollivier, R.; El Ahmad, Y.; Laurent, E. 1,4-Dialkylpiperazine Derivatives, Method for Obtaining them, and Pharmaceutical Compositions Containing them. PCT Int. Appl. WO 93 16,057 (Cl. C07D295/10), 1993; FR Appl. 92/1,843, Feb 1992.
(32) Sasaki, T.; Manamoto K.; Itoh, H. J. Convenient Synthesis of some Purine 8,5′-Iminocyclonucleoside. *J. Org. Chem.* **1978**, *43: 12*, 2320−2325.
(33) Hartung, W. H.; Simonoff, R. Hydrogenolysis of Benzyl Groups Attache to Oxygen, Nitrogen or Sulfur. *Org. React.* **1953**, *VII*, 263−326.
(34) Saxena, Y.; Agarwal, S. K.; Patnaik, G. K.; Saxena, A. K. [β-(Aroylaminoethyl)]piperazines and Piperidines and [2-(Arylaminocarbonyl)ethyl]piperazines, Piperidines, Pyrazino-pyridoindoles; A New Class of Potent H, Antagonists. *J. Med. Chem.* **1990**, *33*, 2970−2976.
(35) Podona, T.; Guardiola-Lemaître, B.; Caignard, D. H.; Adam, G.; Pfeiffer, B.; Renard, P.; Guillaumet, G. 3,4-Dihydro-3-amino-2H-1-benzopyran Derivatives as 5-HT$_{1A}$ Receptor Ligands and Potential Anxiolytic Agents. 1. Synthesis and Structure-Activity Relationship Studies. *J. Med. Chem.* **1994**, *37*, 1779−1793.
(36) McCall, R. B.; Romero, A. G.; Bienkowski, M. J.; Harris, D. W.; McGuire, J. C.; Piercey, M. F.; Shuck, M. E.; Smith, M. W.; Svensson, K. A.; Schereur, P. J. K. D.; Carlsson, A.; Vonvoigtlander, P. F. Characterization of U-92016A as a Selective, Orally Active, High Intrinsic Activity 5-Hydroxytryptamine$_{1A}$ Agonist. J. *Pharmacol. Exp. Ther.* **1994**, *271*, 875−883.
(37) Pauwels, P. J.; Gompel, P. V.; Leysen, J. E. Activity of Serotonin (5-HT) Receptor Agonists, Partial Agonists and Antagonists at Cloned Human 5-HT1A Receptors that are Negatively Coupled to Adenylate Cyclase in Permanently Transfected Hela Cells. *Biochem. Pharmacol.* **1993**, *45* (2), 375−383.
(38) Hall, M.; El Mestikawy, S.; Emesit, M.; Pichat, L.; Hamon, M.; Gozlan, H. [^{3}H]-8-Hydroxy-2(di-n-propylamino)-tetralin Binding to Pre and Post Synaptic 5-Hydroxytryptamine Sites in Various Regions of the Rat Brain. *J. Neurochem.* **1985**, *44*, 1685−1696.
(39) Leysen, J. E.; Niemegeers, C. J. E.; Van Nueten, J. M.; Laduron, P. M. [^{3}H]Ketanserin (R 41 468), a Selective [^{3}H]-Ligand for Serotonin$_2$ Receptor Binding Sites. *Mol. Pharmacol.* **1982**, *21*, 301−314.
(40) Terai, M.; Hidaka, K.; Nakamura, Y. Comparison of [^{3}H] YM09151−2 with [^{3}H]Spiperone and [^{3}H]Raclopride for Dopamine D2 Receptors Binding to Rat Striatum. *Eur. J. Pharmacol.* **1989**, *173*, 177−182.
(41) Greengrass, P.; Bremner, R. Binding Characteristic of [^{3}H]-Prazosin to Rat Brain α-Adrenergic Receptors. *Eur. J. Pharmacol.* **1979**, *55*, 323−326.
(42) Salomon, Y. Adenylate Cyclase Assays. *In Advances in Cyclic Nucleotide Research;* Brooker, G., Greengaard, P., Robinson, G. A., Eds.; Raven Press: New York, 1979; Vol. 110, pp 35−55.
(43) Berendsen, H. H. G.; Jenck, F.; Brockramp, C. L. E. Selective Activation of 5-HT$_{1A}$ Receptors Induced Lower Lip Retraction in the Rat. *Pharmacol. Biochem. Behav.* **1989**, *33*, 821−827.

JM950759Z