# Characterization of Potent and Selective Antagonists at Postsynaptic 5-$HT_{1A}$ Receptors in a Series of N4-Substituted Arylpiperazines

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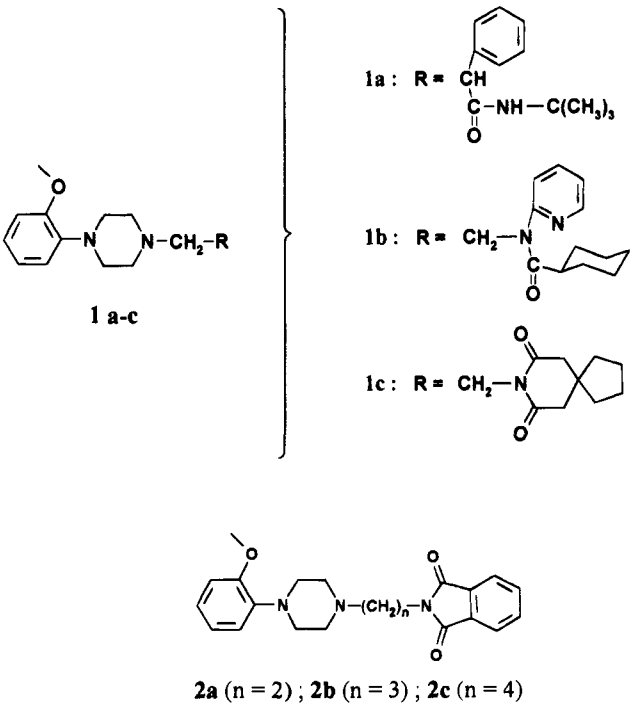
Benzocycloalkyl and benzocycloalkenyl moities linked, directly or via an alkyl chain, to oxygen-bearing heteroarylpiperazines were synthesized, in an attempt to obtain potent and selective antagonists at postsynaptic 5-$HT_{1A}$ receptors. From the numerous arylpiperazines described in the literature, 1-(2,3-dihydro-1,4-benzodioxin-5-yl)piperazine (**3a**) was chosen as a model of an arylpiperazine in view of its selectivity for 5-$HT_{1A}$ receptors versus $\alpha_1$-, $\alpha_2$-, and $\beta$-adrenergic receptors, as well as dopamine $D_1$ and $D_2$ receptors. Two other closely-related arylpiperazines, 1-(1,5-benzodioxepin-6-yl)piperazine (**3b**) and 1-(benzofuran-7-yl)piperazine (**3c**), were also examined in this study. All compounds showed high affinity at 5-$HT_{1A}$ sites ($8.10 \leq pK_i s \leq 9.35$), and the majority behaved as antagonists *in vivo* in blocking the hypothermia induced by the 5-$HT_{1A}$ agonist 8-OH-DPAT in the absence of a marked effect alone at equivalent doses. An *in vivo* evaluation of dopamine $D_2$ receptor antagonist properties revealed that the majority of compounds was devoid of activity at this site, in marked contrast to BMY 7378 which displayed virtually no selectivity for 5-$HT_{1A}$ versus dopamine $D_2$ receptors. Moreover, six compounds of the present series, **8**, **10**, **11**, **14**, **25**, and, **37**, showed >10-fold selectivity *in vitro* for 5-$HT_{1A}$ versus $\alpha_1$-adrenergic receptors. Compound **14** displayed an optimal compromise between potency ($pK_i = 8.75$), marked antagonist activity, and selectivity toward $\alpha_1$-adrenergic (81-fold) and dopamine $D_2$ (195-fold) receptors. These characteristics clearly distinguish **14** from previously-reported ligands such as the postsynaptic 5-$HT_{1A}$ antagonist BMY 7378 and the weak partial agonist NAN 190 which, in contrast to the compounds of this series, belong to the well-exemplified class of imido derivatives of (*o*-methoxyphenyl)piperazines. The availability of **14** (S 15535) should facilitate the further elucidation of the functional role and potential therapeutic significance of 5-$HT_{1A}$ receptors.

## Introduction

While several selective 5-$HT_{1A}$ receptor agonists have been described, for example 8-OH-DPAT, the lack of selectivity of most widely-used "5-$HT_{1A}$ antagonists"—with the apparent exceptions of (**1a**) WAY 100,135 and (**1b**) WAY 100,635—has hampered evaluation of the functional roles of 5-$HT_{1A}$ receptors in the control of mood,[1] motor behavior, nociception, thermoregulation, endocrine secretion, and appetite.[2] Indeed, one major problem confronted in the development of 5-$HT_{1A}$ receptor antagonists is that of "cross talk" to $\alpha_1$-adrenergic receptors,[3] as illustrated by the weak partial agonist NAN 190, 1-(2-methoxyphenyl)-4-[4-(2-phthalimido)-butyl]piperazine, **2c**.[4] Actions at dopamine $D_2$ receptors have also proven difficult to eliminate, for example, BMY 7378, 8-[2-[4-(2-methoxyphenyl)piperazin-1-yl]-ethyl]-8-azaspiro[4.5]decane-7,9-dione, **1c**, a further proposed 5-$HT_{1A}$ receptor antagonist, exhibits pronounced dopamine $D_2$ receptor antagonist properties *in vivo*.[5] An additional important question in the development and characterization of putative 5-$HT_{1A}$ antagonists relates, as discussed by Hjorth[6] and Sharp,[7] to their differential actions at 5-$HT_{1A}$ autoreceptors versus postsynaptic 5-$HT_{1A}$ receptors. Correspondingly, NAN 190 and in particular BMY 7378 exert essentially antagonist actions at postsynaptic sites yet retain some agonist properties at 5-$HT_{1A}$ autoreceptors.

**Chart 1**




The major common chemical feature of compounds **1c** and **2c** (apart from the presence of a cyclic imide) is an (*o*-methoxyphenyl)piperazine. As reported by El Bermawy,[8] "simple arylpiperazines" possess substantial affinity for 5-$HT_{1A}$ sites, and among these, (*o*-methoxy-

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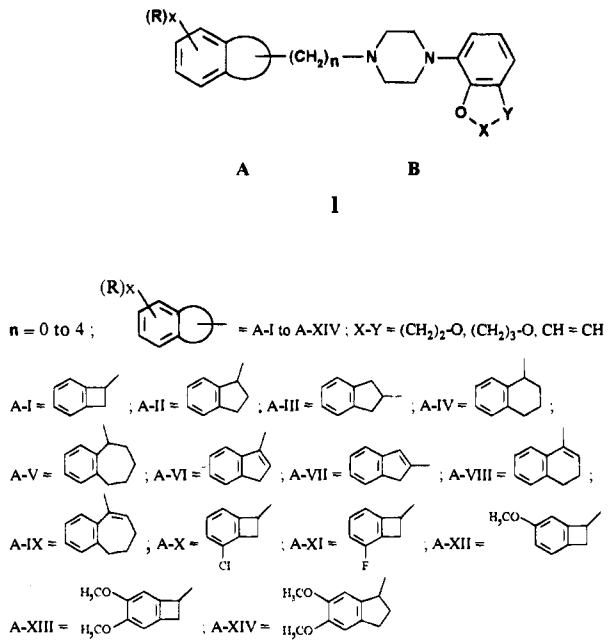
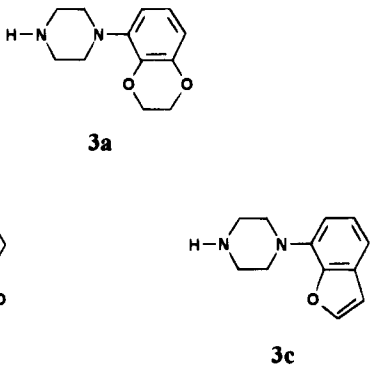
**Chart 2**




phenyl)piperazine is one of the most potent. Interestingly, although numerous arylpiperazines were described in this work, there was no mention of one particular (*o*-methoxyphenyl)piperazine-related structure, that is, 1-(2,3-dihydro-1,4-benzodioxin-5-yl)piperazine, also known as eltoprazine, **3a**, which is a potent agonist at both 5-HT$_{1A}$ autoreceptors and postsynaptic 5-HT$_{1A}$ receptors. Indeed, it appears that comparatively little attention has been paid to this piperazine as a potential chemical starting point for the synthesis of antagonists at postsynaptic 5-HT$_{1A}$ receptors, possibly since eltoprazine also recognizes 5-HT$_{1B}$ sites with high affinity ($pK_i$ = 7.27 for 5-HT$_{1B}$ versus 8.03 for 5-HT$_{1A}$). Nevertheless, the selectivity of eltoprazine for 5-HT$_{1A}$ receptors versus $\alpha_1$-adrenergic and dopamine D$_2$ receptors encouraged us to search for novel, selective antagonists at postsynaptic 5-HT$_{1A}$ receptors lacking marked *in vivo* activity at $\alpha_1$-adrenergic and dopamine D$_2$ receptors and structurally-related to 1-(2,3-dihydro-1,4-benzodioxin-5-yl)piperazine. As it is known that (1) substitution on the N4 piperazine nitrogen atom enhances the affinity of arylpiperazines for 5-HT$_{1A}$ receptors while simultaneously decreasing affinity for 5-HT$_{1B}$ receptors[9] and (2) appendage of a lipophilic group to the amino portion of an agonist structure should generate an antagonist at the same receptor site (Ariens strategy), we prepared a series of compounds possessing the general structure **I** shown in chart 2 in which the N4 piperazine nitrogen was linked directly, or by the virtue of a tether, to benzocycloalkyl or benzocycloalkenyl residues. The A moiety is one of a bicyclic system termed A-I–A-XIV, and the B moiety may be 1-(2,3-dihydro-1,4-benzodioxin-5-yl)piperazine, **3a**, or the closely-related analogs 1-(1,5-benzodioxepin-6-yl)piperazine, **3b**, and 1-(benzofuran-7-yl)piperazine, **3c** (Chart 3).

In the present work, we describe the synthetic methodology used in the preparation of compounds of structure **I** and examine structure–activity relationships on the basis of the results of binding studies at 5-HT$_{1A}$ sites. Further, we illustrate the approach adopted for (a) characterization of *in vivo* antagonist activity at postsynaptic 5-HT$_{1A}$ receptors and (b) determination of

**Chart 3**




*in vivo* selectivity for 5-HT$_{1A}$ receptors versus $\alpha_1$-adrenergic and dopamine D$_2$ receptors. Affinities at $\alpha_1$-adrenergic and dopamine D$_2$ receptors *in vitro* are given for several compounds displaying marked selectivity *in vivo*.

## Chemistry

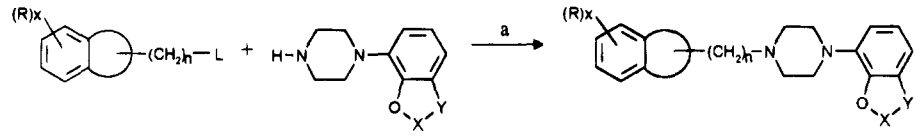
Two pathways (Scheme 1) were used in order to prepare the compounds listed in Tables 1–3. Compounds **7**, **8**, **10**, **14**, **25**, **31**, **32**, **34**, **35**, and **37** were obtained through method A; the reaction between compounds **4a–f** (the characteristics of which are given in Table 4) and the appropriate piperazine (Chart 3) was conducted upon reflux of toluene or methyl isobutyl ketone (MIBK) with yields ranging from 20% to 87%. The remainder of the compounds were formed using method B. Coupling between the appropriate acid derivatives **5a–u** (Table 4) and compounds **3a–c** (Chart 3), using carbonyldiimidazole (CDI), led to intermediate amides **6a–u** (Scheme 1, Tables 1–3) which were reduced by LiAlH$_4$ in THF; the overall yields (two steps) ranged from 16% to 69%. Piperazines **3a–c** were synthesized according to a known procedure depicted in Scheme 2.

## Biology

The biological characterization of the compounds prepared in the present work was based upon an experimental strategy fully discussed previously.[5] The 5-HT$_{1A}$ and 5-HT$_{1B}$ affinities of the compounds listed in Tables 1–3 were assessed respectively by inhibition of the binding of [$^3$H]-8-OH-DPAT in rat hippocampal membranes and by inhibition of the binding of [$^3$H]-5-HT (in the presence of 8-OH-DPAT and mesulergine) in rat frontal cortex membranes.[10] The ability of compounds to inhibit the decrease of core temperature elicited by sc administration of 8-OH-DPAT in rats (Table 5) was employed as a measure of antagonism at postsynaptic 5-HT$_{1A}$ receptors.[11] Minimal effective doses (MEDs) required to inhibit the action of 8-OH-DPAT (antagonist effect) were compared to the doses needed to elicit hypothermia upon administration alone (agonist effect); these MEDs were defined relative to the corresponding vehicle ($P < 0.05$ in Dunnett's test following ANOVA). Ratios of MED agonist to MED antagonist were calculated (Table 5). In addition, the maximal percentage agonist and antagonist effects for respectively inducing hypothermia and blocking the action of 8-OH-DPAT were determined (Table 5). The activities of compounds at $\alpha_1$-adrenergic and dopamine D$_2$ receptors were determined respectively in the models

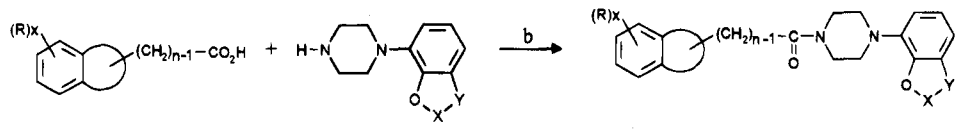
**Scheme 1**[a]

Method A ( n = 0 to 4, L = OMs, OTs, Br or I)

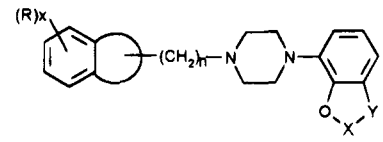


4 a-f 3 a-c I (7, 8, 10, 14, 25, 31, 32, 34, 35, 37)

Method B ( n = 1 to 4)



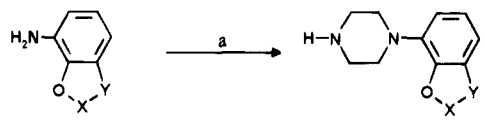
5 a-u 3 a-c 6 a-u



I (9, 11-13, 15-24, 26-30, 33, 36)

[a] Reagents and conditions: (a) methyl isobutyl ketone or toluene, $Na_2CO_3$, Δ; (b) CDI, $CH_2Cl_2$; (c) $LiAlH_4$, THF.

**Scheme 2**[a]



38 a-c 3 a-c

X-Y is $(CH_2)_2$-O in **38 a** ; $(CH_2)_3$-O in **38 b** ; CH = CH in **38 c** ; **3 a-c** : chart **3**

[a] Reagents and conditions: (a) $HN(CH_2CH_2Cl)_2$, chlorobenzene, $K_2CO_2$, Δ.

of modulation of palpebral aperture ($ED_{50}$ for induction of ptosis)[12] and inhibition of the stereotyped gnawing induced by the dopamine releaser methylphenidate ($ID_{50}$ for inhibiting of gnawing)[13] (Table 6). Selectivity for 5-$HT_{1A}$ receptors over $\alpha_1$-adrenergic and dopamine $D_2$ receptors was also estimated by determination of affinity ratios at 5-$HT_{1A}$ versus $\alpha_1$ and $D_2$ sites depicted in Table 7. For $\alpha_1$ sites, inhibition of [$^3$H]prazosin binding in rat cortex and for $D_2$ sites inhibition of [$^3$H]spiperone binding in rat striatium were measured.[5]

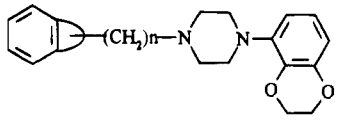
## Results

**Structure–Activity Relationships.** Unsubstituted benzocycloalkyl and benzocycloalkenyl derivatives of 1-(2,3-dihydro-1,4-benzodioxin-5-yl)piperazine (Table 1)-displayed pronounced affinity for 5-$HT_{1A}$ receptors. In distinction, the substituted benzocyclobutanes **25**, **28**, and **29** (Table 2) manifested a reduced affinity in comparison to their unsubstituted analog **8**. The same tendency was observed with 3-Cl benzocyclobutane derivatives **24** and **26** which were less potent than their respective unsubstituted analogs **7** and **9**. Nevertheless, the 3-F derivative **27** and the 5,6-di-OMe deriative **30** were equipotent to their unsubstituted analogs **7** and **12**. It is, thus, difficult to make general inferences from this pattern of substitution, although it appears that substitutions on the phenyl ring do not enhance affinity at 5-$HT_{1A}$ sites. However, it appears that the size of the ring attached to the phenyl ring in the A moiety may be of greater importance in determining affinity. Compounds **18** and **19**, which bear respectively a six- and a seven-membered ring, were among the least potent compounds of the series in terms of their affinity at 5-$HT_{1A}$ receptors, and it is reasonable to conclude, on the basis of the behavior of **8**, **12**, **18**, and **19**, that an increase in the size of the cycloalkyl ring is correlated with a decrease in affinity at 5-$HT_{1A}$ sites. Regarding the unsaturation on the A moiety, the unsaturated compounds **20**–**23** revealed slightly but consistently greater affinity at 5-$HT_{1A}$ sites than their saturated analogs **12**, **16**, **18**, and **19**.

As concerns the nature of the aryl part of the B moiety, replacement in **8** or **9** of the 2,3-dihydro-1,4-benzodioxin-5-yl residue by a 1,5-benzodioxepin-6-yl or benzofuran-7-yl residue yielded respectively **32**, **33**, **35**, and **36** (Table 3) which displayed lower affinities at 5-$HT_{1A}$ sites. The behavior of the compounds in this series yields, thus, the following order of potency: 2,3-dihydro-1,4-benzodioxin-5-yl > 1,5-benzodioxepin-6-yl > benzofuran-7-yl.

With respect to the influence of the length of the spacer between the arylpiperazine and the A moiety, **7**, **11**, **15**, and **31** in which $n = 1$ were less potent than **8**, **12**, **16**, and **32**, their analogs where $n = 2$, and **9**, **13**, **17**, and **33**, their analogs where $n = 3$. Further, **10**, where $n = 4$, and **14**, where $n = 0$, were more potent than **7**

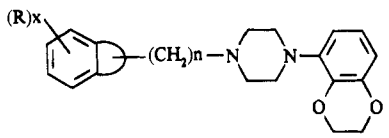
**Table 1.** Unsubstituted Benzocycloalkyl and Benzocycloalkenyl Derivatives of 1-(2,3-Dihydro-1,4-benzodioxin-5-yl)piperazine (Physical properties and affinities at 5-HT$_{1A}$ and 5-HT$_{1B}$ sites)



| compd | a | n | starting materials (intermediate amides) | method | yield (%) | mp (°C)[b] | recryst solvent[c] | formula[d] | pK$_i$[f] 5-HT$_{1A}$ | pK$_i$[f] 5-HT$_{1B}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| **7** | A-I | 1 | **4a/3a** | A | 30 | 91–95 | iPr$_2$O | $C_{21}H_{24}N_2O_2$ | 8.75 ± 0.05 | 6.67 ± 0.02 |
| **8** | A-I | 2 | **4b/3a** | A | 49 | 224–226 | EtOH | $C_{22}H_{26}N_2O_2$·HCl | 9.23 ± 0.05 | 6.22 ± 0.01 |
| **9** | A-I | 3 | **5a/3a (6a)** | B | 16 | 206–208 | EtOH | $C_{23}H_{28}N_2O_2$·HCl | 9.35 ± 0.06 | 6.19 ± 0.05 |
| **10** | A-I | 4 | **4c/3a** | A | 44 | 180–183 | EtOH | $C_{24}H_{30}N_2O_2$·$C_4H_4O_4$[e] | 8.89 ± 0.01 | 6.20 ± 0.08 |
| **11** | A-II | 1 | **5g/3a (6b)** | B | 34 | 87–90 | H$_2$O | $C_{22}H_{26}N_2O_2$ | 8.76 ± 0.03 | 6.70 ± 0.11 |
| **12** | A-II | 2 | **5h/3a (6c)** | B | 41.5 | 220–222 | CH$_3$CN | $C_{23}H_{28}N_2O_2$·HCl | 8.80 ± 0.04 | 6.38 ± 0.04 |
| **13** | A–II | 3 | **5i/3a (6d)** | B | 62 | 175–185 | Et$_2$O | $C_{24}H_{30}N_2O_2$·2HCl | 9.21 ± 0.02 | 6.69 ± 0.14 |
| **14** | A–III | 0 | **4e/3a** | A | 33 | 168–171 | Et$_2$O | $C_{21}H_{24}N_2O_2$ | 8.75 ± 0.03 | 5.75 ± 0.03 |
| **15** | A-III | 1 | **5k/3a (6e)** | B | 52.5 | 232–234 | Et$_2$O | $C_{22}H_{26}N_2O_2$·HCl | 8.55 ± 0.06 | 6.31 ± 0.02 |
| **16** | A-III | 2 | **5l/3a (6f)** | B | 69 | 121–123 | CH$_3$CN | $C_{23}H_{28}N_2O_2$ | 9.18 ± 0.01 | 6.16 ± 0.08 |
| **17** | A-III | 3 | **5m/3a (6g)** | B | 52 | 210–211 | H$_2$O | $C_{24}H_{30}N_2O_2$·HCl | 8.90 ± 0.14 | 5.73 ± 0.12 |
| **18** | A-IV | 2 | **5n/3a (6h)** | B | 40 | 250–252 | CH$_3$CN | $C_{24}H_{30}N_2O_2$·HCl | 8.56 ± 0.08 | 6.15 ± 0.01 |
| **19** | A-V | 2 | **5o/3a (6i)** | B | 29 | 179–186 | CH$_3$OH | $C_{25}H_{32}N_2O_2$·2HCl | 8.18 ± 0.05 | 6.11 ± 0.01 |
| **20** | A-VI | 2 | **5p/3a (6j)** | B | 30 | 254–256 | CH$_3$OH | $C_{23}H_{26}N_2O_2$·HCl | 9.10 ± 0.07 | 6.60 ± 0.06 |
| **21** | A-VII | 2 | **5q/3a (6k)** | B | 42 | >260 | CH$_3$CN | $C_{23}H_{26}N_2O_2$·HCl | 9.27 ± 0.01 | 6.03 ± 0.13 |
| **22** | A-VIII | 2 | **5r/3a (6l)** | B | 52 | 203–210 | EtOH | $C_{24}H_{28}N_2O_2$·HCl | 8.70 ± 0.01 | 6.64 ± 0.05 |
| **23** | A-IX | 2 | **5s/3a (6m)** | B | 55 | 233–236 | EtOH | $C_{25}H_{30}N_2O_2$·HCl | 8.50 ± 0.14 | 6.42 ± 0.15 |
| **1a** (WAY 100,135) | | | | | | | | | 7.49 ± 0.01 | <5 |
| **1c** (BMY 7378) | | | | | | | | | 8.71 ± 0.11 | <5 |
| **2c** (NAN 190) | | | | | | | | | 9.15 ± 0.06 | 5.97 ± 0.01 |
| **3a** (eltoprazine) | | | | | | | | | 8.03 ± 0.04 | 7.27 ± 0.02 |

[a] See Chart 2. [b] All melting points were determined on a Reichert Thermovar apparatus and are uncorrected. [c] iPr$_2$O, disopropyl ether; EtOH, ethanol; CH$_3$CN, acetonitrile; Et$_2$O, diethyl ether; AcOEt, ethyl acetate. [d] Compounds were purified by column chromatography; C, H, and N analyses were within 0.4% of theoretical values for the formulae given, unless otherwise stated. All compounds exhibited NMR consistent with assigned structures. [e] Fumaric acid. [f] pK$_i$ ± SEM values are based on two to five assays.

**Table 2.** Substituted Benzocycloalkyl Derivatives of 1-(2,3-Dihydro-1,4-benzodioxin-5-yl)piperazine (Physical properties and affinities at 5-HT$_{1A}$ and 5-HT$_{1B}$ sites)



| compd | (R)x a | n | starting materials (intermediate amides) | method | yield (%) | mp (°C)[b] | recryst solvent[c] | formula[d] | pK$_i$[f] 5-HT$_{1A}$ | pK$_i$[f] 5-HT$_{1B}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| **24** | A-X | 1 | **5b/3a (6n)** | B | 29 | >260 | H$_2$O | $C_{21}H_{23}ClN_2O_2$·HCl | 8.40 ± 0.05 | 6.26 ± 0.01 |
| **25** | A-X | 2 | **4d/3a** | A | 75 | 207–211 | CH$_3$CN | $C_{21}H_{23}ClN_2O_2$·2HCl | 8.65 ± 0.01 | 6.15 ± 0.02 |
| **26** | A-X | 3 | **5c/3a (6o)** | B | 45 | 223–226 | CH$_3$CN | $C_{23}H_{27}ClN_2O_2$·2HCl | 8.43 ± 0.02 | 5.96 ± 0.01 |
| **27** | A-XI | 1 | **5d/3a (6p)** | B | 45 | 254–256 | H$_2$O | $C_{21}H_{23}FN_2O_2$·HCl | 8.75 ± 0.01 | 6.50 ± 0.05 |
| **28** | A-XII | 2 | **5e/3a (6q)** | B | 62 | 192–194 | H$_2$O | $C_{23}H_{28}N_2O_3$·HCl | 8.90 ± 0.06 | 6.50 ± 0.01 |
| **29** | A-XIII | 2 | **5f/3a (6r)** | B | 59 | 232–234 | H$_2$O | $C_{24}H_{30}N_2O_4$·HCl | 8.50 ± 0.02 | 6.10 ± 0.04 |
| **30** | A-XIV | 2 | **5j/3a (6s)** | B | 25 | 225–226 | CH$_3$OH | $C_{26}H_{32}N_2O_4$·HCl | 8.80 ± 0.06 | 6.17 ± 0.01 |

[a–d,f] See corresponding footnotes of Table 1.

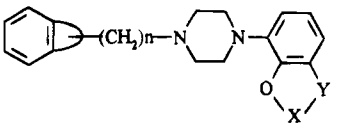
and **15**, their analogs with $n = 1$. It is of interest to note that highest affinities were always obtained where $n = 2$ or 3, with **9** being the most potent compound of the presently-described series and, in fact, one of most potent ligands at 5-HT$_{1A}$ sites as yet described. Consequently, from Tables 1–3, it can be concluded that affinity for 5-HT$_{1A}$ sites corresponds to the following order of potency: $n = 2$ or $3 > n = 0$ or $4 > n = 1$.

Finally, as concerns selectivity toward other 5-HT receptor sites, each of the compounds examined, in marked contrast to eltoprazine, exhibited ≥100-fold preference for 5-HT$_{1A}$ versus 5-HT$_{1B}$ sites (Tables 1–3). In addition, selectivity was >100-fold versus 5-HT$_{2A}$, 5-HT$_{2C}$, and 5-HT$_3$ sites (data not shown).

**Biological Results.** From Table 5, it can be concluded that the majority of compounds behaved as antagonists in preventing the hypothermia induced by 8-OH-DPAT with ID$_{50}$s below or close to 1.0 mg/kg, sc. Further, they displayed their antagonist activity at doses well below those at which agonist activity was seen, and all, except **7**, **9**, **13**, and **37**, exerted a greater maximal antagonist that agonist effect (Table 5). For example, **12**, **14**, **16**, **19**, **20**, **22**, **24**, **25**, **28**, and **29**, which are derivatives of **1**-(2,3-dihydro-1,4-benzodioxin-5-yl), all showed >90% antagonism of 8-OH-DPAT. Similarly, the 1,5-benzodioxepin-6-yl derivative **31** and the benzofuran-7-yl derivatives **34** and **35** showed >90% inhibition of the action of 8-OH-DPAT.

In the methylphenidate-induced gnawing test (Table 6), the majority of compounds failed to reverse gnawing, even at doses as high as 40 mg/kg, sc. In contrast, the dopamine D$_2$ receptor antagonist haloperidol blocked

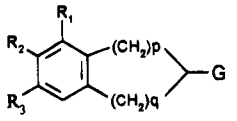
**Table 3.** Other Piperazine Derivatives (Physical properties and affinities at 5-$HT_{1A}$ and 5-$HT_{1B}$ sites)

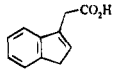
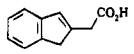
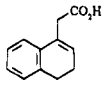


| compd | [a] | n | X–Y | starting materials (intermediate amides) | method | yield (%) | mp (°C)[b] | recryst solvent[c] | formula[d] | p$K_i$[f] 5-$HT_{1A}$ | p$K_i$[f] 5-$HT_{1B}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **31** | A-I | 1 | $(CH_2)_3$-O | **4f/3b** | A | 37 | 248–252 | EtOH | $C_{22}H_{26}N_2O_2$·HCl | 8.10 ± 0.09 | NT |
| **32** | A-I | 2 | $(CH_2)_3$-O | **4b/3b** | A | 87 | 170–172 | EtOH | $C_{23}H_{26}N_2O_2$·HCl | 8.94 ± 0.01 | 6.25 ± 0.04 |
| **33** | A-I | 3 | $(CH_2)_3$-O | **5a/3b (6t)** | B | 37 | 262–265 | EtOH | $C_{24}H_{30}N_2O_2$·HCl | 9.10 ± 0.12 | 6.21 ± 0.05 |
| **34** | A-I | 1 | HC=CH | **4f/3c** | A | 65 | 202–204 | AcOEt | $C_{21}H_{22}N_2O$·2HCl | 8.10 ± 0.05 | 6.04 ± 0.10 |
| **35** | A-I | 2 | HC=CH | **4b/3c** | A | 47 | 192–195 | iPrOH | $C_{24}H_{22}N_2O$·HCl | 8.85 ± 0.04 | 5.82 ± 0.04 |
| **36** | A-I | 3 | HC=CH | **5a/3c (6u)** | B | 47 | 197–200 | $CH_3OH$ | $C_{23}H_{26}N_2O$·$C_4H_4O_4$[e] | 8.55 ± 0.06 | 5.85 ± 0.02 |
| **37** | A-III | 0 | $(CH_2)_3$-O | **4e/3b** | A | 20 | 138–140 | $Et_2O$ | $C_{22}H_{26}N_2O_2$ | 8.42 ± 0.03 | 5.85 ± 0.06 |

[a–f] See corresponding footnotes of Table 1. NT = not tested.

**Table 4.** Starting Materials: Benzocycloalkanes and Benzocycloalkenes (Physical properties)



| compd | $R_1$ | $R_2$ | $R_3$ | *p* | *q* | G | mp (°C)[b] | recryst solvent[c] | formula[d] |
|---|---|---|---|---|---|---|---|---|---|
| **4a** | H | H | H | 1 | 0 | $CH_2I$ | oil | | $C_9H_9I$ |
| **4b** | H | H | H | 1 | 0 | $(CH_2)_2Br$ | oil | | $C_{10}H_{11}Br$ |
| **4c** | H | H | H | 1 | 0 | $(CH_2)_4OMs$ | oil | | $C_{13}H_{18}O_3S$ |
| **4d** | Cl | H | H | 1 | 0 | $(CH_2)_2Br$ | oil | | $C_{10}H_{10}ClBr$ |
| **4e** | H | H | H | 1 | 1 | OTs | 119–120 | $H_2O$ | $C_{16}H_{16}O_3S$ |
| **4f** | H | H | H | 1 | 0 | $CH_2OTs$ | oil | | $C_{16}H_{16}O_3S$ |
| **5a** | H | H | H | 1 | 0 | $(CH_2)_2CO_2H$ | amorph | | $C_{11}H_{12}O_2$ |
| **5b** | Cl | H | H | 1 | 0 | $CO_2H$ | 105–110 | $CH_3CN$ | $C_9H_7ClO_2$ |
| **5c** | Cl | H | H | 1 | 0 | $(CH_2)_2CO_2H$ | oil | | $C_{11}H_{11}ClO_2$ |
| **5d** | F | H | H | 1 | 0 | $CO_2H$ | 176–178 | $CH_3CN$ | $C_9H_7FO_2$ |
| **5e** | H | H | OMe | 1 | 0 | $CH_2CO_2H$ | 137–140 | $Et_2O$ | $C_{11}H_{12}O_3$ |
| **5f** | H | OMe | OMe | 1 | 0 | $CH_2CO_2H$ | 136–139 | $Et_2O$ | $C_{12}H_{14}O_4$ |
| **5g** | H | H | H | 0 | 2 | $CO_2H$ | 50–55 | EtOH | $C_{10}H_{10}O_2$ |
| **5h** | H | H | H | 0 | 2 | $CH_2CO_2H$ | 63–64 | EtOH | $C_{11}H_{12}O_2$ |
| **5i** | H | H | H | 0 | 2 | $(CH_2)_2CO_2H$ | 49–50 | | $C_{13}H_{16}O_2$ |
| **5j** | H | OMe | OMe | 0 | 2 | $CH_2CO_2H$ | 153–155 | $H_2O$ | $C_{13}H_{16}O_4$ |
| **5k** | H | H | H | 1 | 1 | $CO_2H$ | 128–130 | $H_2O$ | $C_{10}H_{10}O_2$ |
| **5l** | H | H | H | 1 | 1 | $CH_2CO_2H$ | 86–87 | EtOH | $C_{11}H_{12}O_2$ |
| **5m** | H | H | H | 1 | 1 | $(CH_2)_2CO_2H$ | 75–78 | $H_2O$ | $C_{12}H_{14}O_2$ |
| **5n** | H | H | H | 0 | 3 | $CH_2CO_2H$ | amorph | | $C_{12}H_{14}O_2$ |
| **5o** | H | H | H | 0 | 4 | $CH_2CO_2H$ | 98–99 | AcOEt | $C_{13}H_{16}O_2$ |
| **5p** |  | | | | | | 74–76 | $Et_2O$ | $C_{11}H_{10}O_2$ |
| **5q** |  | | | | | | 121–123 | $H_2O$ | $C_{11}H_{10}O_2$ |
| **5r** |  | | | | | | amorph | | $C_{12}H_{12}O_2$ |
| **5s** |  | | | | | | 95–96 | $iPr_2O$ | $C_{13}H_{14}O_2$ |

[b–d] See corresponding footnotes of Table 1.

gnawing with an $ID_{50}$ of 0.02 mg/kg, sc, an action mimicked by BMY 7378 ($ID_{50}$ = 0.65 mg/kg, sc) and less potently, by **9**, **16**, and **33**.

In the test of palpebral aperture (Table 6), ptosis was induced by the prototypical $\alpha_1$-adrenergic receptor antagonist prazosin with an $ED_{50}$ of 0.04 mg/kg, sc. NAN 190 also potently elicited ptosis over a similar dose range, and each compound listed in Table 6 was less potent in this paradigm than NAN 190. Three compounds, **14**, **36**, and **37**, were devoid of activity, while **25** was only weakly active and **10**, **11**, **18**, **30**, and **32** showed comparable potency to BMY 7378. It is worth noting that benzocycloalkyl compounds, for example, **12** and **18**, were less active at $\alpha_1$-adrenergic receptors than their benzocycloalkenyl analogs **20** and **22**.

## Discussion and Conclusion

By introducing lipophilic bicyclic substituants on the N4 piperazine nitrogen atom of "simple arylpiperazines" structurally different from the widely-used (*o*-methoxyphenyl)piperazine, we have demonstrated that it is possible to obtain potent and selective antagonists at 5-$HT_{1A}$ receptors. Interestingly, compounds **I** were devoid of the cyclic imide or amide group present in the

**Table 5.** Postsynaptic 5-HT$_{1A}$ Antagonism *in Vivo* (Core temperature)

| compd | ID$_{50}$ (mg/kg, sc) (95% CL) | MED (mg/kg, sc) | | MED(agonist)/ MED(antagonist) | max effect[a] (%) (dose, mg/kg, sc) | |
|---|---|---|---|---|---|---|
| | | agonist | antagonist | | agonist | antagonist |
| **7** | 0.67 (0.26–1.70) | 10 | 0.63 | 15.8 | 100 (40) | 85 (2.5) |
| **8** | 0.65 (0.36–1.14) | 40 | 1.25 | 32 | 32 (40) | 76 (2.5) |
| **9** | 0.18 (0.05–0.66) | 10 | 0.16 | 62.5 | 100 (40) | 75 (0.63) |
| **10** | 1.43 (0.51–3.97) | >10 | 5 | >2 | 0 (10) | 88 (5.0) |
| **11** | 1.32 (0.63–2.76) | 10 | 0.63 | 15.8 | 43 (10) | 63 (2.5) |
| **12** | 1.29 (0.5–2.4) | >40 | 0.63 | >63.5 | 19 (40) | 94 (40) |
| **13** | 0.29 (0.09–0.92) | 10 | 0.16 | 62.5 | 100 (10) | 81 (2.5) |
| **14** | 1.4 (0.7–2.9) | 20 | 0.63 | 31.7 | 46 (20) | 95 (10) |
| **15** | 0.55 (0.23–1.33) | >10 | 0.63 | >15.8 | 0 (10) | 87 (2.5) |
| **16** | 0.27 (0.15–0.50) | 10 | 0.16 | 62.5 | 50 (10) | 100 (2.5) |
| **17** | 0.47 (0.37–0.61) | 40 | 0.63 | 63.5 | 40 (40) | 70 (0.63) |
| **18** | 0.40 (0.06–2.59) | >2.5 | 0.16 | >15.6 | 8 (2.5) | 70 (2.5) |
| **19** | 4.26 (2.62–6.91) | >10 | 5 | >2 | 9 (10) | 96 (10) |
| **20** | 0.45 (0.07–2.85) | >2.5 | 0.63 | >4 | 21 (2.5) | 94 (2.5) |
| **21** | 0.36 (0.23–0.57) | 10 | 0.31 | 32.2 | 76 (40) | 81 (0.63) |
| **22** | 0.40 (0.16–1.03) | >40 | 0.63 | >63.5 | 14 (40) | 100 (10) |
| **23** | 5.02 (0.18–1.33) | >40 | 2.5 | >16 | 33 (40) | 55 (10) |
| **24** | 0.80 (0.08–7.81) | 40 | 0.63 | 63.5 | 0 (10) | 100 (10) |
| **25** | 1.13 (0.50–2.57) | 40 | 1.25 | 32 | 52 (40) | 96 (10) |
| **26** | 3.09 (1.08–8.84) | >10 | 0.63 | >15.8 | 15 (10) | 60 (10) |
| **27** | 2.51 (0.38–16.45) | >10 | 0.63 | >15.8 | 19 (10) | 61 (10) |
| **28** | 0.48 (0.23–0.97) | 10 | 0.63 | 15.8 | 35 (40) | 95 (1.25) |
| **29** | 1.41 (0.62–3.19) | >40 | 1.25 | >32 | 4 (40) | 96 (10) |
| **30** | 0.86 (0.42–1.74) | >40 | 2.5 | >16 | 12 (40) | 84 (2.5) |
| **31** | 0.32 (0.08–1.21) | >10 | 0.63 | >15.8 | 76 (40) | 91 (2.5) |
| **32** | 2.68 (1.37–5.25) | 40 | 1.25 | 32 | 31 (20) | 72 (10) |
| **33** | 0.27 (0.05–1.38) | >2.5 | 0.16 | >15.6 | 21 (2.5) | 85 (2.5) |
| **34** | 1.12 (0.41–3.03) | >10 | 2.5 | >4 | 15 (10) | 96 (10) |
| **35** | 1.12 (0.32–3.85) | >40 | 1.25 | >32 | 21 (40) | 91 (10) |
| **36** | ≈2.5 | 10 | 2.5 | 4 | 46 (10) | 47 (2.5) |
| **37** | 5.18 (1.65–16.15) | 10 | 5 | 2 | 72 (10) | 51 (5.0) |
| **1a** (WAY 100,135) | 2.45 (0.97–6.18) | 40 | 2.5 | 16 | 50 (40) | 73 (10) |
| **1c** (BMY 7378) | 1.60 (0.87–2.94) | 2.5 | 1.25 | 2 | 53 (10) | 64 (2.5) |
| **2c** (NAN 190) | 0.97 (0.2–4.6) | 5 | 0.63 | 7.9 | 100 (10) | 56 (2.5) |
| **3a** (eltoprazine) | >40.0 | 2.5 | >40.0 | <0.06 | 100 (40) | 0 (40) |

[a] Maximum agonist effect is expressed relative to 8-OH-DPAT (100%), and maximum antagonist effect is expressed relative to basal values before injection of 8-OH-DPAT (100%).

majority of proposed 5-HT$_{1A}$ antagonists (NAN 190, BMY 7378, MDL 73005 EF, spiperone, WAY 100,135, and WAY 100,635). The use in the A moiety of simple bicyclic systems such as benzocyclobutane, indane,

Table 6. Activities at $\alpha_1$-Adrenergic and Dopamine $D_2$ Receptors (Induction of palpebral aperture and inhibition of methylphenidate-indced gnawing)[a]

| compd | palpebral aperture: induction of ptosis $ED_{50}$ (mg/kg, sc) (95% CL) | inhibition of methylphenidate-induced gnawing $ID_{50}$ (mg/kg, sc) (95% CL) |
|---|---|---|
| **7** | 0.70 (0.40–1.24) | >40 |
| **8** | 4.85 (2.39–9.83) | >40 |
| **9** | 0.45 (0.13–1.58) | 1.70 (0.63–4.60) |
| **10** | 7.15 (2.95–17.3) | >40 |
| **11** | ≃5 | >40 |
| **12** | 4.01 (2.58–6.23) | >40 |
| **13** | 0.23 (0.15–0.35) | >40 |
| **14** | >40 | >40 |
| **15** | ≃5 | >40 |
| **16** | 0.66 (0.36–1.22) | 5.90 (1.60–9.85) |
| **17** | 1.73 (0.81–3.70) | >40 |
| **18** | ≃5 | 40 |
| **19** | >2.5 | >10 |
| **20** | ≃0.3 | >40 |
| **21** | 0.17 (0.09–0.32) | NT |
| **22** | ≃1.25 | >40 |
| **23** | >2.5 | 40 |
| **24** | ≃5 | >40 |
| **25** | ≃20.0 | >40 |
| **26** | ≃1.25 | 40 |
| **27** | >1.25 | >40 |
| **28** | ≃1.25 | >40 |
| **29** | ≃1.25 | >40 |
| **30** | ≃10 | 40 |
| **31** | <2.5 | >40 |
| **32** | 6.96 (2.31–20.90) | ≃30 |
| **33** | 0.24 (0.16–0.37) | 1.14 (0.62–2.08) |
| **34** | ≃2.5 | NT |
| **35** | >2.5 | >40 |
| **36** | >40 | 40 |
| **37** | >40 | >40 |
| **1a** (WAY 100,135) | >40 | >40 |
| **1c** (BMY 7378) | 6.47 (2.69–15.50) | 0.65 (0.20–2.16) |
| **2c** (NAN 190) | 0.051 (0.017–0.150) | 10.01 (4.87–20.60) |
| haloperidol | 0.81 (0.31–2.57) | 0.02 (0.01–0.05) |
| prazosin | 0.04 (0.02–0.11) | >10 |

[a] NT = not tested; ≃ = approximative (based on two doses), $ED_{50}$ not precisely calculable.

tetralin, and benzocycloheptane (and their unsaturated analogs indene, dihydronaphthalene, and benzocycloheptene) allowed us to study in detail the influence of a number of substituents on the phenyl ring and of the size of the nonaromatic cycle of the bicyclic system upon affinity at 5-$HT_{1A}$ sites. As the general tendency was a slight decrease in affinity upon the introduction of substituents on to benzocyclobutane and indane, we next examined the influence of the size of the bicyclic system in nonsubstituted benzocycloalkyl and benzocycloalkenyl derivatives (Figure 1). Here, the results were more striking since, between the benzocyclobutane **8** and its analog benzocycloheptane **19**, the fall in affinity at 5-$HT_{1A}$ receptors was greater than 10-fold. Even if this difference appeared to be less pronounced in the case of benzocycloalkenyl compounds, it is evident that an increase in the size of the cycle joined to the phenyl ring is deleterious for affinity at 5-$HT_{1A}$ sites, as shown in Figure 1 with the four 2-(benzocycloalkan-1-yl)ethyl analogs **8**, **12**, **18**, and **19** on one hand the three 2-(benzocycloalken-1-yl)ethyl analogs **20**, **22**, and **23** on the other. Although little attention has been directed toward this aspect in the literature and comparisons of the size of the cyclic substituants within the same series of arylpiperazines have not been frequently reported, Yocca[14] demonstrated that enlarging the cyclopentyl ring of buspirone to its cyclohexyl equivalent

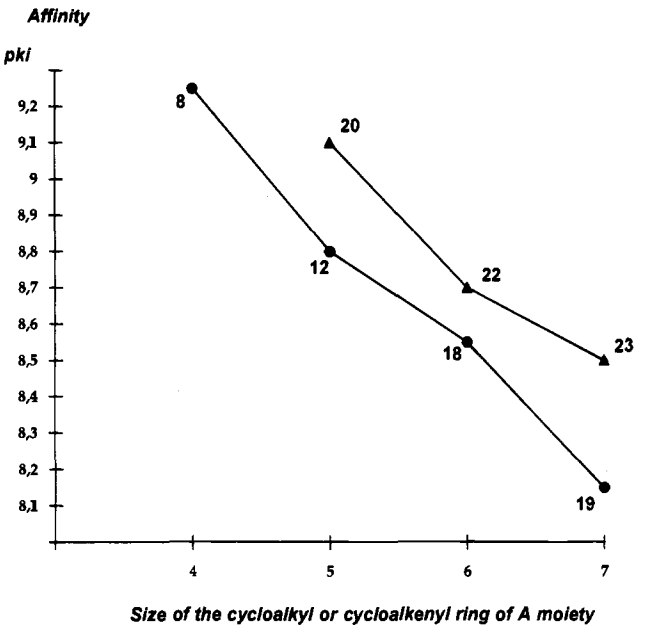



**Figure 1.** Influence of the size of the cycloalkyl and cycloalkenyl rings on affinity at 5-$HT_{1A}$ sites for benzocycloalkyl (●) and benzocycloalkenyl (▲) derivatives of 1-(2,3-dihydro-1,4-benzodioxin-5-yl)piperazine. Data were taken from Table 1 and are expressed as the $pK_i$ determined by displacing [$^3$H]-8-OH-DPAT from 5-$HT_{1A}$ sites in rat hippocampal membranes for compounds **8**, **12**, **18**, **19** and **20**, **22**, **23**.

augmented affinity at 5-$HT_{1A}$ receptors. This finding contrasts, evidently, to our observations and is of particular interest in that busipirone belongs to the family of cyclic imide compounds.

A further interesting difference to previously-described series was that variation of the length of the tether between the A moiety and the piperazine did not modify affinity (Figure 2) to the same extent as observed by Glennon[15] in his study of NAN 190 derivatives (Chart 1, compounds **2a**–**2c**). In the latter case, affinity was highly dependent upon chain length with compounds for which $n = 2$ (**2a**), 3 (**2b**), and 4 (**2c**) showing affinities of 990, 20, and 0.6 nM, respectively. In the present series, for the same arylpiperazine (1-(2,3-dihydro-1,4-benzodioxin-5-yl)piperazine) and the same benzocycloalkane, (indan-2-yl or benzocyclobutan-1-yl), a variation of $n$ from 0 to 3 or from 1 to 4, respectively, only slightly affected affinity (a maximal difference of 0.63 $pK_i$ was seen between **15** and **16**) (Figure 2). Similarly, El Bermawy[16] reported that, in a series of phenylalkyl derivatives of (*o*-methoxyphenyl)piperazine, there was little change in affinity at 5-$HT_{1A}$ sites upon varying the length of the alkyl chain from 2 to 5. Interestingly, as regards a series of BMY 7378-related agents, Yocca[14] reported a still different pattern of findings: affinity was maximal for $n = 4$ and 2 (BMY 7378), whereas the derivative for which $n = 3$ was 10 times less potent. It may, therefore, be concluded that the influence of chain length on affinity is highly dependent upon the nature of the terminal residue, though in the case of "desamido" derivatives (compounds **I** and El Bermawy compounds),[16] chain length does not play a decisive role in determining affinity at 5-$HT_{1A}$ receptors.

On the other hand, the nature of the arylpiperazine does appear to exert an influence on affinity, in that the preferred piperazine in this study was the 1-(2,3-dihydro-1,4-benzodioxin-5-yl)piperazine (highest $pK_i$ val-

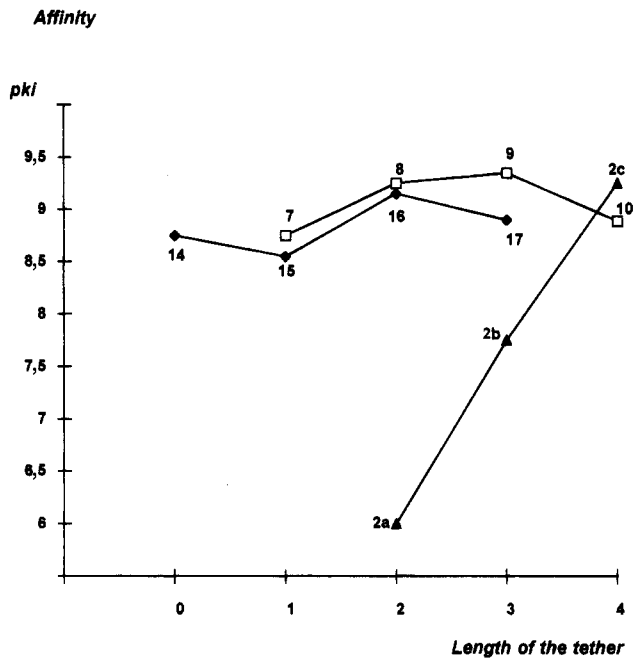



**Figure 2.** Variation of p$K_i$ as a function of the length of the tether for indan-2-yl derivatives (◆) and benzocyclobutan-1-yl derivatives (□) in comparison to NAN 190 derivatives (▲). Data were taken from Table 1 and are expressed as the p$K_i$ determined by displacing [$^3$H]-8-OH-DPAT from 5-HT$_{1A}$ sites in rat hippocampal membranes for compounds **7**–**10** and **14**–**17**. For NAN 190 derivatives **2a**–**c**, data were adapted from ref 15.

ues in the series were obtained for **8** and **9**), whereas 1-(benzofuran-7-yl)piperazine always conferred lower affinity (see **35** and **36**, the analogs of **8** and **9**). In the work of Van Steen,[17] which compared a series of N4-alkyl derivatives of these two piperazines, the conclusion was somewhat different since, for lower alkyl derivatives, the piperazine giving the highest affinities was 1-(benzofuran-7-yl)piperazine, but for higher alkyl derivatives (*n*-hexyl, *n*-octyl, and *n*-decyl), 1-(2,3-dihydro-1,4-benzodioxin-5-yl)piperazine inferred maximal affinity.

In addition, as previously pointed out by Glennon,[9] we demonstrate herein that substitution on the piperazine N4 nitrogen atom enhances the affinity of "simple arylpiperazines" (such as **3a**) for 5-HT$_{1A}$ receptors (each derivative of **3a** tested displayed affinity for 5-HT$_{1A}$ sites superior to that of eltoprazine) and lowers that for 5-HT$_{1B}$ sites, resulting in compounds with high selectivity for 5-HT$_{1A}$ versus 5-HT$_{1B}$ sites (Tables 1 and 2).

As previously noted,[3] there is still a need for 5-HT$_{1A}$ receptor antagonists of superior selectivity in order to more fully characterize the physiological roles of 5-HT$_{1A}$ receptors. Attempts to meet this requirement have been made by a number of authors, including El Bermawy,[16] Glennon,[15] and Raghupathi.[18] Working on different series of derivatives of (*o*-methoxyphenyl)piperazine, they concentrated mainly on selectivity toward $\alpha_1$-adrenergic receptors, but affinity at dopamine D$_2$ receptors was not disclosed. More recently, Perrone[19] proposed a series of dihydronaphthalene derivatives of arylpiperazines displaying some selectivity over dopamine D$_2$ receptors, but selectivity versus $\alpha_1$-adrenergic receptors was not examined. As shown in Table 6, a number of compounds of the general structure **I** display limited activity *in vivo* at $\alpha_1$-adrenergic and dopamine

**Table 7.** Affinities and Selectivities *in Vitro*: 5-HT$_{1A}$ vs $\alpha_1$-Adrenergic and 5-HT$_{1A}$ vs Dopamine D$_2$

| | p$K_i$[a] | | selectivity, $K_i$ ratio[b] | |
|---|---|---|---|---|
| compd | $\alpha_1$ | D$_2$ | $\alpha_1$/5-HT$_{1A}$ | D$_2$/5-HT$_{1A}$ |
| **8** | 7.66 ± 0.03 | 7.31 ± 0.01 | 35.4 | 79.4 |
| **10** | 7.56 ± 0.10 | 7.71 ± 0.03 | 17.8 | 12.5 |
| **11** | 7.75 ± 0.04 | 7.38 ± 0.03 | 18.6 | 43.6 |
| **14** | 6.84 ± 0.09 | 6.46 ± 0.04 | 81 | 195 |
| **25** | 7.19 ± 0.08 | 7.22 ± 0.01 | 28.8 | 26.9 |
| **30** | 7.81 ± 0.10 | 6.88 ± 0.06 | 9.8 | 83.4 |
| **37** | 6.68 ± 0.01 | 6.71 ± 0.03 | 55.0 | 51.3 |
| **1a** (WAY 100,135) | 5.94 ± 0.01 | 6.41 ± 0.01 | 35.6 | 12.0 |
| **1c** (BMY 7378) | 6.74 ± 0.05 | 7.76 ± 0.04 | 93.3 | 8.9 |
| **2c** (NAN 190) | 9.09 ± 0.02 | 7.50 ± 0.04 | 1.15 | 44.7 |

[a] p$K_i$s ± SEMs are derived from two to five determinations. [b] $K_i$ values for 5-HT$_{1A}$ receptors are calculated from Tables 1–3.

D$_2$ receptors. As shown in Tables 6 and 7, the majority of the compounds of the series showed a marked (>10-fold) selectivity toward dopamine D$_2$ receptors *in vitro* and *in vivo* (irrespective of the nature of the A or B moiety in contrast to BMY 7378, which displays virtually no selectivity toward dopamine D$_2$ receptors *in vivo*). Moreover, six compounds of the present series, **8**, **10**, **11**, **14**, **25**, and **37**, showed >10-fold selectivity *in vitro* for 5-HT$_{1A}$ versus $\alpha_1$-adrenergic sites (Table 7). Of these, **14** and **37** (each lacking a tether between the A moiety and the arylpiperazine) attained the highest level of selectivity, inasmuch as they were devoid of *in vivo* activity at $\alpha_1$-adrenergic receptors (Table 6), in line with their low binding affinity at this site (Table 7). In contrast, as noted by Van Wijngaarden,[20] NAN 190 was almost equipotent at 5-HT$_{1A}$ and $\alpha_1$-adrenergic receptors both *in vitro* and *in vivo*.

As concerns the apparent efficacy of ligand actions at postsynaptic 5-HT$_{1A}$ receptors, according to the criteria adopted herein, in which a hypothermia model was employed, the majority of compounds **I** showed lower partial agonist properties than BMY 7378 and NAN 190, a finding confirmed in several further tests for **8**, **12**, and **14**.[5] These findings with hypothermia are of importance since this parameter is highly sensitive to weak partial agonists.[21] Further, as all the derivatives of **3a** act as antagonists at postsynaptic 5-HT$_{1A}$ receptors (Table 5), in distinction to eltoprazine **3a**, which behaves as an agonist, the present study represents a successful implementation of the Ariens strategy of receptor antagonist design via appendage of a lipophilic group to the amino portion of a receptor agonist structure.

In conclusion, this novel series of arylpiperazines led to the characterization of several potent 5-HT$_{1A}$ ligands, in particular the 1-(2,3-dihydro-1,4-benzodioxin-5-yl)-piperazine derivatives **8**, **9**, **13**, **16**, and **21**. Further, several compounds (**10**, **15**, **18**, **19**, **24**, and **29**) behaved as antagonists with only low (<10%) partial agonist activity at postsynaptic 5-HT$_{1A}$ sites *in vivo*. Finally, *in vivo* activities at $\alpha_1$-adrenergic and dopamine D$_2$ receptors (Table 6) were virtually absent for **14** (a derivative of **3a**), **36** (a derivative of **3c**), and **37** (a derivative of **3b**) and only weak for **25** and **30**, conferring on these products a level of selectivity more pronounced than apparent for BMY 7378 and NAN 190, in good agreement with their affinities and selectivities *in vitro* (Table 7).

Overall, **14** showed the best compromise between potency ($pK_i$ = 8.75), marked antagonist action, and selectivity toward $\alpha_1$-adrenergic and dopamine $D_2$ receptors *in vitro* (≥80) and *in vivo* (>28.5). Interestingly, **14** retains agonist activity at 5-$HT_{1A}$ autoreceptors (data not shown) in contrast to WAY 100,135, which is also a selective 5-$HT_{1A}$ ligand (though less potent: $pK_i$ = 7.49) but displays antagonist activity at 5-$HT_{1A}$ autoreceptors.[22] Consequently, the availability of **14** should facilitate the further characterization of the functional roles and therapeutic significance of 5-$HT_{1A}$ receptors.

## Experimental Section

**Chemistry.** Reactions performed in nonaqueous solvents were carried out under an atmosphere of nitrogen. Column chromatography was carried out with Merck Kieselgel 60 (230–400 mesh) under a nitrogen pressure of 0.5 atm. Microanalyses were performed on solid samples only, with a Carlo Erba autoanalyzer. IR spectra were recorded on a Bruker IF 548 infrared spectrometer. $^1$H NMR were recorded on either a Bruker AC 200 or Bruker AM 400 spectrometer at 200 and 400 MHz, respectively. Chemical shifts are reported as $\delta$ values in parts per million (ppm) relative to tetramethylsilane ($\delta$ 0.00) used as an internal standard. Benzocyclobutane derivatives **4a–d,f** and **5a–f** were obtained by classical methods through their corresponding 1-cyanobenzocyclobutane precursors, readily obtainable according to the method described in details by Klundt[23] and Kametani.[24–26] The other benzocycloalkyl and benzocycloalkenyl derivatives are described in the literature.

**Starting Materials. 1-(2,3-Dihydro-1,4-benzodioxin-5-yl)piperazine, Hydrochloride (3a, HCl).** A suspension of **38a** (63 g, 0.42 mmol), potassium carbonate (60.6 g, 0.42 mol), and bis(chloroethyl)amine hydrochloride (78.5 g, 0.42 mol) in chlorobenzene (0.945 L) was stirred under reflux for 24 h. The reaction mixture was poured in water (1 L), and after decantation of the organic layer, the aqueous layer was twice extracted by $Et_2O$ (200 mL). The aqueous layer was treated with 2 N NaOH (250 mL) and extracted with AcOEt (3 × 250 mL). The combined extracts were dried ($MgSO_4$), and after evaporation, the residue was taken up in $CH_3CN$ (375 mL). The careful addition of a 3 N HCl etheral solution (90 mL) led to the hydrochloride salt: 58 g (54%); mp >260 °C; $^1$H NMR (DMSO-$d_6$) 3.2 (br s, 8H, $CH_2$ pip), 4.2 (m, 4H, $OCH_2CH_2O$), 6.5 (dd, 1H), 6.6 (dd, 1H), 6.75 (t, 1H), 9.3 (s, 2H, $NH_2^+$).

**3b,c, HCl. 3b,c** were obtained according to the same method starting respectively from 6-amino-1,5-benzodioxepin and 7-aminobenzo[*b*]furan.

**1-(1,5-Benzodioxepin-6-yl)piperazine, hydrochloride (3b, HCl):** $^1$H NMR ($D_2O$) 2.2 (m, 2H, $OCH_2CH_2CH_2O$), 3.65 and 3.8 (2m, 8H, $CH_2$ pip), 4.2 and 4.3 (2t, 4H, $OCH_2CH_2CH_2O$), 7.0–7.2 (m, 3H, Ar).

**1-(Benzofuran-7-yl)piperazine, hydrochloride (3c, HCl):** $^1$H NMR (DMSO-$d_6$) 3.1 (m, 4H $(CH_2)_2NH$), 3.3 (m, 4H, $(CH_2)_2NAr$), 5.45 (br, 2H, $NH_2^+$), 6.75 (d, 1H), 6.9 (d, 1H, OCH=CH), 7.1–7.3 (m, 2H), 7.95 (d, 1H, OCH=CH).

**General Method A. 1-(2,3-Dihydro-1,4-benzodioxin-5-yl)-4-(benzocyclobutan-1-ylmethyl)piperazine (7).** A suspension of compound **4a** (4 g, 16 mmol), compound **3a** (3.6 g, 16.2 mmol), and sodium carbonate (6.95 g, 65 mmol) in methyl isobutyl ketone (100 mL) was stirred under reflux for 24 h. After evaporation of the solvent, the residue was taken up in dichloromethane (150 mL) and washed with $H_2O$ (50 mL); the organic layer was extracted with 1 N HCl (3 × 50 mL), and the combined aqueous acid extracts was basified with 2 N NaOH (100 mL). The separated organic layer was taken up in $CH_2Cl_2$ and then dried ($MgSO_4$) and concentrated under reduced pressure. The solid obtained (4.4 g) was recrystallized from diisopropyl ether: yield 1.6 g (30%); mp 91–95 °C; $^1$H NMR ($CDCl_3$) 2.65 (dd, 1H, HCHCH-endo), 2.7 (m, 4H, $CH_2$ pip), 2.85 (m, 2H, $CH_2N$), 3.10 (m, 4H, $CH_2$ pip), 3.4 (dd, 1H, HCH-CH endo), 3.7 (m, 1H, $H_2CCH$ endo), 4.3 (m, 4H, $OCH_2CH_2O$), 6.6 (m, 2H, Bzd H-6,8), 6.8 (t, 1H, Bzd H-7), 7.0–7.3 (m, 4H, arom).

The following compounds (**8**, **10**, **14**, **25**, **31**, **32**, **34**, **35**, and **37**) were prepared according to the reaction reported as method A.

**1-(2,3-Dihydro-1,4-benzodioxin-5-yl)-4-(2-benzocyclobutan-1-ylethyl)piperazine, hydrochloride (8):** $^1$H NMR (DMSO-$d_6$) 2.2 (m, 2H, $CH_2CH_2N$), 2.85 (dd, 1H, HCHCH endo), 3.0–3.7 (cluster of 12H, 1H, $CH_2CH$ end + 8H, $CH_2$ pip + 2H, $CH_2CH_2N$ + 1H, HCHCH endo), 4.25 (m, 4H, $OCH_2CH_2O$), 6.4–6.7 (2d, 2H, Bzd H-6,8), 6.75 (t, 1H, Bzd H-7), 7.1–7.3 (m, 4H, arom), 11.6 (br, 1H, $NH^+$).

**4-(4-Benzocyclobutan-1-ylbutyl)-1-(2,3-dihydro-1,4-benzodioxin-5-yl)piperazine, fumarate (10):** $^1$H NMR (DMSO-$d_6$) 1.35–1.75 (m, 6H, $HC(CH_2)_3CH_2N$), 2.55 (t, 2H, $(CH_2)_3CH_2N$), 2.65 (dd, 1H, HCHCH endo), 2.7 (m, 4H, $CH_2$ pip), 3.05 (m, 4H, $CH_2$ pip), 3.25 (dd, 1H, HCHCH endo), 3.4 (m, 1H, $CH_2CH$ endo), 4.2 (m, 4H, $OCH_2CH_2O$), 6.55 (m, 2H, Bzd H-6,8), 6.6 (s, 2H, HC=CH fum), 6.7 (t, 1H, Bzd H-7), 7.0–7.2 (m, 4H, arom), 8.0 (br, 2H, $NH^+$).

**1-(2,3-Dihydro-1,4-benzodioxin-5-yl)-4-(indan-2-yl)piperazine (14):** $^1$H NMR ($CDCl_3$) 3–3.5 (cluster of 12H, 8H, $CH_2$ pip + 4H, $CH_2CHCH_2$ ind), 3.85 (m, 1H, $CH_2CHCH_2$ ind), 4.3 (m, 4H, $OCH_2CH_2O$), 6.45 and 6.6 (2dd, 2H, Bzd H-6,8), 6.75 (t, 1H, Bzd H-7), 7.2 (s, 4H, arom).

**4-[2-(3-Chlorobenzocyclobutan-1-yl)ethyl]-1-(2,3-dihydro-1,4-benzodioxin-5-yl)piperazine, dihydrochloride (25):** $^1$H NMR (DMSO-$d_6$) 2.2 (m, 2H, $CH_2CH_2N$), 2.9 (dd, 1H, HCHCH endo), 3.0–3.3 (cluster of 5H, 1H, $CHCH_2$ endo + 4H, $CH_2$ pip), 4.2 (m, 4H, $OCH_2CH_2O$), 6.5 (m, 2H, Bzd H-6,8), 6.75 (t, 1H, Bzd, H-7), 7.2 (m, 4H, arom), 11.4 (br, 2H, $NH^+$).

**4-(Benzocyclobutan-1-ylmethyl)-1-(1,5-benzodioxepin-6-yl)piperazine, hydrochloride (31):** $^1$H NMR ($CDCl_3$) 2.8 (m, 2H, $OCH_2CH_2CH_2O$), 3.0–3.8 (cluster of 11H, 1H, $CH_2CH$ endo + 2H, $(HCH)_2N$ pip + 1H, HCHCH endo, 6H, $CHCH_2N(CH_2)_2$ pip + 1H, HCHCH endo), 4.25 (cluster of 6H, 4H, $OCH_2CH_2O$ + 2H, $(HCH)_2N$ pip), 6.5–6.7 (m, 2H, Bzd H-7,9), 6.8 (t, 1H, Bzd H-8), 7.0–7.3 (m, 4H, arom), 13.0 (br, 1H, $NH^+$).

**4-(2-Benzocyclobutan-1-ylethyl)-1-(1,5-benzodioxepin-6-yl)piperazine, hydrochloride (32):** $^1$H NMR (DMSO-$d_6$) 2.1 (cluster of 4H, 2H, $OCH_2CH_2CH_2O$ + 2H, $CH_2CH_2N$), 2.8 (dd, 1H, HCHCH endo), 3.0–3.7 (cluster of 12H, 4H, $CH_2$ pip + 1H, $CHCH_2$ endo + 1H, HCHCH endo + 6H, $H_2CCH_2N(CH_2)_2$ pip), 4.1 (m, 4H, $OCH_2CH_2CH_2O$), 6.6 (m, 2H, Bzd H-7,9), 6.9 (m, 1H, Bzd H-8), 7.0–7.3 (m, 4H, arom), 11.3 (br, 1H, $NH^+$).

**4-(Benzocyclobutan-1-ylmethyl)-1-benzofuran-7-ylpiperazine, dihydrochloride (34):** $^1$H NMR (DMSO-$d_6$) 3.1–3.8 (cluster of 10H, 2H, $CH_2CH$ endo + 8H, $CH_2$ pip), 3.95 (d, 2H, $CHCH_2N$), 4.1 (m, 1H, $CHCH_2$ endo), 6.85 (d, 1H, Bzf H-6), 6.9 (d, 1H, OCHCH), 7.1–7.3 (cluster of 6H, 4H arom + 2H Bzf H-4,5), 7.75 (br, 1H, $NH^+$), 7.95 (d, 1H, OCHCH), 11.9 (br, 1H, $NH^+$).

**4-(2-Benzocyclobutan-1-ylethyl)-1-benzofuran-7-ylpiperazine, hydrochloride (35):** $^1$H NMR ($CDCl_3$) 2.4 (m, 2H, $CH_2CH_2N$), 2.9 (dd, 1H, HCHCH endo), 3.2 (m, 4H, $CH_2$ pip), 3.45 (dd, 1H, HCHCH endo), 3.5–4 (cluster of 7H, 4H, $CH_2$ pip + 1H, $CH_2CH$ endo + 2H, $CH_2CH_2N$), 6.8 (m, 2H, Bzf H-3,6), 7.0–7.4 (cluster of 6H, 4H, arom + 2H, Bzf H-4,5), 7.6 (d, 1H, Bzf H-2), 13.05 (br, 1H, $NH^+$).

**1-(1,5-Benzodioxepin-6-yl)-4-indan-2-ylpiperazine (37):** $^1$H NMR ($CDCl_3$) 2.2 (q, 2H, $OCH_2CH_2CH_2O$), 2.7 (m, 4H, $CH_2$ pip), 2.8–3.2 (m, 4H, $CH_2CHCH_2$ ind), 3.25 (m, 4H, $CH_2$ pip), 3.3 (m, 1H, $CH_2CHCH_2$ ind), 4.2 (m, 4H, $OCH_2CH_2CH_2O$), 6.6 (m, 2H, H-7,9), 6.8 (t, 1H, Bzd H-8), 7.15 (m, 4H, arom).

**General Method B. 4-(3-Benzocyclobutan-1-ylpropyl)-1-(2,3-dihydro-1,4-benzodioxin-5-yl)piperazine, Hydrochloride (9).** Carbonyldiimidazole (6.7 g, 41 mmol) was added under stirring to a solution of compound **5a** (7.5 g, 42 mmol) dissolved in methylene chloride (75 mL). After the end of gaseous evolution (≈2 h), compound **3a** (9.8 g, 44 mmol) dissolved in $CH_2Cl_2$ (25 mL) was added dropwise in 5 min. The mixture was stirred overnight at room temperature and evaporated to dryness and the residue taken up in $Et_2O$ (100 mL) and extracted by 1 N HCl (3 × 75 mL). The combined aqueous acid extracts were basified with 2 N NaOH (100 mL) in the presence of ethyl acetate (250 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure.

The crude product was purified by column chromatography ($CH_2Cl_2$/AcOEt, 9:1) to afford 5.9 g (39%) of the amide **6a** as an oil. A solution of **6a** (5.9 g, 15.1 mmol) in THF (100 mL) was added dropwise to a suspension of $LiAlH_4$ (0.6 g, 15.8 mmol) in THF (20 mL). After 2 h at room temperature, the mixture was treated with $H_2O$ (0.41 mL), NaOH (0.33 mL), and then $H_2O$ (1.5 mL). After filtration and evaporation, the residue was purified by column chromatography ($CH_2Cl_2$/MeOH, 95:5). The hydrochloride was obtained by adding 1 N HCl (22 mL) dropwise to a solution of the free base in $Et_2O$ (40 mL). After stirring from 30 min, the precipitate was filtered off and dried on vacuum under KOH: yield 16%; mp 206–208 °C; $^1$H NMR (DMSO-$d_6$) 1.7 (m, 2H, C$H_2$(CH$_2$)$_2$N), 2.0 (m, 2H, CH$_2$C$H_2$CH$_2$N), 2.75 (dd, 1H *H*CHCH endo), 3.15 (cluster of 6H, 4H, C$H_2$ pip + 2H, (CH$_2$)$_2$C$H_2$N), 3.3 (dd, 1H, HC*H*CH endo), 3.4–3.7 (cluster of 5H, 1H, CH$_2$C*H* endo + 4H, C$H_2$ pip), 4.2 (s, 4H, OC$H_2$C$H_2$O), 6.5 (m, 2H, Bzd, H-6,8), 6.75 (t, 1H, Bzd H-7), 7.0–7.3 (m, 4H, arom), 11.35 (br, 1H, NH$^+$).

The following compounds (**11**–**13**, **15**–**24**, **26**–**30**, **33**, and **36**) were prepared, from intermediate amides **6b**–**u**, according to method B.

**1-(2,3-Dihydro-1,4-benzodioxin-5-yl)-4-(indan-1-ylmethyl)piperazine (11):** eluted with $CH_2Cl_2$/AcOEt, 90:10; $^1$H NMR ($CDCl_3$) 1.85 (m, 1H, *H*CHCH ind), 2.3 (m, 1H, HC*H*CH ind), 2.5 (dd, 1H, *H*CHN), 2.7 (cluster of 5H, 4H, C$H_2$ pip + 1H, HC*H*N), 2.85 (m, 2H, C$H_2$CH$_2$CH ind), 3.15 (m, 4H, C$H_2$ pip), 3.4 (m, 1H, CH$_2$CH$_2$C*H*N ind), 4.3 (m, 4H, OC$H_2$C$H_2$O), 6.55 (m, 2H, Bzd H-6,8), 6.8 (t, 1H, Bzd H-7), 7.1–7.5 (m, 4H, arom).

**1-(2,3-Dihydro-1,4-benzodioxin-5-yl)-4-(2-indan-1-ylethyl)piperazine, hydrochloride (12):** eluted with $CH_2Cl_2$/AcOEt, 90:20; $^1$H NMR (DMSO-$d_6$) 1.6–2.3 (cluster of 4H, 2H, C$H_2$CH$_2$N + 2H, CH$_2$C$H_2$CH ind), 2.85 (m, 2H, CH$_2$C$H_2$N), 3.0–3.3 (cluster of 7H, 4H, C$H_2$ pip + 1H, CH$_2$CH$_2$C*H* ind + 2H, C$H_2$CH$_2$CH ind), 3.5 (n, 4H, (C$H_2$)$_2$ pip), 4.2 (m, 4H, OC$H_2$C$H_2$O), 6.5 (m, 2H, Bzd H-6,8), 6.75 (t, 1H, Bzd H-7), 7.25 (m, 4H, arom), 11.1 (br, 1H, NH$^+$).

**1-(2,3-Dihydro-1,4-benzodioxin-5-yl)-4-(3-indan-1-ylpropyl)piperazine, dihydrochloride (13):** eluted with $CH_2Cl_2$/AcOEt, 90:10; $^1$H NMR (DMSO-$d_6$) 1.4 (m, 1H, *H*CHCH$_2$-CH$_2$N), 1.6 (m, 1H, CH$_2$*H*CHCH ind), 1.8 (cluster of 3H, 2H, CH$_2$C$H_2$CH$_2$N + 1H, HC*H*CH$_2$CH$_2$N), 2.25 (m, 1H, CH$_2$HC*H*CH$_2$ ind), 2.85 (m, 1H, CH$_2$CH$_2$C*H* ind), 2.95–3.3 (cluster of 8H, 2H, C$H_2$CH$_2$CH ind + 4H, C$H_2$ pip + 2H, CH$_2$-CH$_2$C$H_2$N), 3.55 (m, 4H, C$H_2$ pip), 4.25 (m, 4H, OC$H_2$C$H_2$O), 6.55 (m, 2H, Bzd H-6,8), 6.8 (t, 1H, Bzd H-7), 7.2 (m, 4H, arom), 11.3 (br, 2H, NH$_2^+$).

**1-(2,3-Dihydro-1,4-benzodioxin-5-yl)-4-(indan-2-ylmethyl)piperazine, hydrochloride (15):** eluted with $CH_2Cl_2$/AcOEt, 90:10; $^1$H NMR (DMSO-$d_6$) 2.7–3.7 (cluster of 15H, 8H, C$H_2$ pip + 4H, C$H_2$CHC$H_2$ ind + 2H, C$H_2$N + CH$_2$CHCH$_2$ ind), 4.3 (s, 4H, OC$H_2$C$H_2$O), 6.55 (m, 2H, Bzd H-6,8), 6.75 (t, 1H, Bzd H-7), 7.2 (m, 4H, arom), 10.9 (br, 1H, NH$^+$).

**1-(2,3-Dihydro-1,4-benzodioxin-5-yl)-4-(2-indan-2-ylethyl)piperazine (16):** eluted with $CH_2Cl_2$/AcOEt, 90:10; $^1$H NMR ($CDCl_3$) 1.75 (m, 2H, C$H_2$CH$_2$N), 2.3–2.8 (cluster of 9H, 4H, C$H_2$ pip + 2H, (*H*CH)$_2$CH ind + 2H, CH$_2$C$H_2$N + (CH$_2$)$_2$C*H* ind), 2.9–3.2 (cluster of 6H, 4H, C$H_2$ pip + 2H, (CH*H*)$_2$CH ind), 4.25 (m, 4H, OC$H_2$C$H_2$O), 6.55 (m, 2H, Bzd H-6,8), 6.75 (t, 1H, Bzd H-7), 7.15 (m, 4H, arom).

**1-(2,3-Dihydro-1,4-benzodioxin-5-yl)-4-(3-indan-2-ylpropyl)piperazine, hydrochloride (17):** eluted with $CH_2Cl_2$/AcOEt, 95:5; $^1$H NMR (DMSO-$d_6$) 1.5 (m, 2H, C$H_2$CH$_2$CH$_2$N), 1.85 (m, 2H, CH$_2$C$H_2$CH$_2$N), 2.40 (m, 1H, CH$_2$C*H*CH$_2$ ind), 2.5–3 (m, 4H, C$H_2$CHC$H_2$ nd), 3.15 (cluster of 6H, 2H, CH$_2$CH$_2$C$H_2$N + 4H, C$H_2$ pip), 3.5 (m, 4H, C$H_2$ pip), 4.2 (m, 4H, OC$H_2$C$H_2$O), 6.55 (m, 2H, Bzd H-6,8), 6.75 (t, 1H, Bzd H-7), 7.10 (m, 4H, arom), 10.8 (br, 1H, NH$^+$).

**1-(2,3-Dihydro-1,4-benzodioxin-5-yl)-4-[2-(1,2,3,4-tetrahydronaphthalen-1-yl)ethyl]piperazine, hydrochloride (18):** eluted with $CH_2Cl_2$/AcOEt, 95:5; $^1$H NMR (DMSO-$d_6$) 1.65–1.85 (m, 4H, CH$_2$C$H_2$C$H_2$CH endo), 2.05–2.25 (m, 2H, C$H_2$CH$_2$N), 2.75 (m, 2H, C$H_2$CH$_2$CH$_2$CH endo), 2.90 (m, 1H, CH$_2$CH$_2$CH$_2$C*H* endo), 3.15 (cluster of 6H, 2H, CH$_2$C$H_2$N + 4H, C$H_2$ pip), 3.5 (m, 4H, C$H_2$ pip), 4.25 (s, 4H, OC$H_2$C$H_2$O), 6.5 (m, 2H, Bzd H-6,8), 6.7 (m, 1H, Bzd H-7), 7.05–7.2 (m, 4H, arom), 11.35 (br, 1H, NH$^+$).

**4-(2-Benzocycloheptan-1-ylethyl)-1-(2,3-dihydro-1,4-benzodioxin-5-yl)piperazine, dihydrochloride (19):** $^1$H NMR (DMSO-$d_6$) 1.4–2.0 (m, 6H, CH$_2$(C$H_2$)$_3$CH endo), 2.0–2.4 (m, 2H, C$H_2$CH$_2$N), 2.7–3.15 (cluster of 5H, 2H, CH$_2$C$H_2$N + 2H, C$H_2$(CH$_2$)$_3$CH endo + 1H, (CH$_2$)$_4$C*H* endo), 3.2 (m, 4H, C$H_2$ pip), 3.3–3.7 (m, 4H, C$H_2$ pip), 4.25 (m, 4H, OC$H_2$C$H_2$O), 6.55 (m, 2H, Bzd H-6,8), 6.8 (t, 1H, Bzd H-7), 7.15 (m, 4H, arom), 11.5 (br, 2H, NH$_2^+$).

**1-(2,3-Dihydro-1,4-benzodioxin-5-yl)-4-(2-inden-3-ylethyl)piperazine, hydrochloride (20):** eluted with $CH_2Cl_2$/AcOEt, 90:10; $^1$H NMR (DMSO-$d_6$) 3.0–3.8 (cluster of 14H, 2H, C$H_2$CH$_2$N + 2H, CH$_2$C$H_2$N + 2H, C$H_2$CH endo + 8H, C$H_2$ pip), 4.2 (m, 4H, OC$H_2$C$H_2$O), 6.4 (br s, 1H, C*H* vinyl), 6.55 (m, 2H, Bzd H-6,8), 6.75 (t, 1H, Bzd H-7), 7.1–7.55 (m, 4H, arom), 11.4 (br, 1H, NH$^+$).

**1-(2,3-Dihydro-1,4-benzodioxin-5-yl)-4-(2-inden-2-ylethyl)piperazine, hydrochloride (21):** eluted with $CH_2Cl_2$/AcOEt, 90:10; $^1$H NMR (DMSO-$d_6$) 2.9–3.4 (cluster of 6H, 4H, C$H_2$ pip + 2H, C$H_2$CH$_2$N), 3.3–3.7 (cluster of 8H, 4H, C*H* pip + 2H, CH$_2$C$H_2$N + 2H, C$H_2$ endo), 4.25 (m, 4H, OC$H_2$C$H_2$O), 6.4–6.6 (m, 2H, Bzd H-6,8), 6.7 (s, 1H, C*H* vinyl), 6.75 (t, 1H Bzd H-7), 7.1–7.45 (m, 4H, arom), 11.45 (br, 1H, NH$^+$).

**1-(2,3-Dihydro-1,4-benzodioxin-5-yl)-4-[2-(1,2-dihydronaphthalen-4-yl)ethyl]piperazine, hydrochloride (22):** $^1$H NMR (DMSO-$d_6$) 2.2 (q, 2H, CH$_2$C$H_2$CH endo), 2.7 (t, 2H, C$H_2$CH$_2$CH endo), 3.0 (m, 2H, C$H_2$CH$_2$N), 3.2 (m, 2H, CH$_2$C$H_2$N), 3.25 (m, 4H, C$H_2$ pip), 3.5–3.7 (m, 4H, C$H_2$ pip), 4.25 (s, 4H, OC$H_2$C$H_2$O), 6.0 (t, 1H, C*H* vinyl), 6.55 (m, 2H, Bzd H-6,8), 6.75 (t, 1H, H-7), 7.15–7.5 (m, 4H, arom), 11.6 (br, 1H, NH$^+$).

**4-(2-Benzocyclohepten-5-ylethyl)-1-(2,3-dihydro-1,4-benzodioxin-5-yl)piperazine, hydrochloride (23):** $^1$H NMR ($CDCl_3$) 1.85 (quad, 2H, CH$_2$CH$_2$C$H_2$CH endo), 2.15 (quint, 2H, CH$_2$C$H_2$CH$_2$CH endo), 2.55 (t, 2H, CH$_2$CH$_2$CH$_2$CH endo), 2.55 (quint, 2H, CH$_2$C$H_2$CH$_2$CH endo), 2.55 (t, 2H, C$H_2$CH$_2$CH$_2$-CH endo), 3.05 (m, 4H, C$H_2$ pip), 3.25 (m, 2H, CH$_2$C$H_2$N), 3.55 (cluster of 6H, 2H, C$H_2$CH$_2$N + 4H, C$H_2$ pip), 4.25 (m, 4H, OC$H_2$C$H_2$O), 6.15 (t, 1H, C*H* vinyl), 6.55 and 6.65 (2d, 2H, Bzd H-6,8), 6.8 (t, 1H, Bzd H-7), 7.25 (m, 4H, arom), 12.8 (br, 1H, NH$^+$).

**4-[(3-Chlorobenzocyclobutan-1-yl)methyl]-1-(2,3-dihydro-1,4-benzodioxin-5-yl)piperazine, hydrochloride (24):** eluted with $CH_2Cl_2$/AcOEt, 90:10; $^1$H NMR (DMSO-$d_6$) 3.1–3.8 (cluster of 12H, 8H, C$H_2$ pip + 2H, C$H_2$CH endo + 2H, C$H_2$N), 4.0 (m, 1H, CH$_2$C*H* endo), 4.25 (m, 4H, OC$H_2$C$H_2$O), 6.55 (m, 2H, Bzd H-6,8), 6.75 (t, 1H, H-7), 7.25 (m, 3H, arom), 11.25 (br, 1H, NH$^+$).

**4-[3-(3-Chlorobenzocyclobutan-1-yl)propyl)]-1-(2,3-dihydro-1,4-benzodioxin-5-yl)piperazine, dihydrochloride (26):** eluted with $CH_2Cl_2$/AcOEt, 90:10; $^1$H NMR (DMSO-$d_6$) 1.7 (m, 2H, C$H_2$CH$_2$CH$_2$N), 1.95 (m, 2H, CH$_2$C$H_2$CH$_2$N), 2.8 (dd, 1H, *H*CHCH endo), 3.15 (cluster of 6H, 2H, CH$_2$CH$_2$C$H_2$N + 4H, C$H_2$ pip), 3.35 (dd, 1H, HC*H*CH endo), 3.4–3.6 (cluster of 5H, 1H, CH$_2$C*H* endo + 4H, C$H_2$ pip), 4.25 (m, 4H, OC$H_2$C$H_2$O), 6.4 (br, 1H, NH$^+$), 6.55 (m, 2H, Bzd H-6,8), 6.75 (t, 1H, H-7), 7.2 (m, 3H, arom), 11.3 (br, 1H, NH$^+$).

**1-(2,3-Dihydro-1,4-benzodioxin-5-yl)-4-[(3-fluorobenzocyclobutan-1-yl)methyl]piperazine, hydrochloride (27):** eluted with $CH_2Cl_2$/AcOEt, 90:10; $^1$H NMR (DMSO-$d_6$) 3.0–3.8 (cluster of 12H, 2H, C$H_2$CH endo + 8H, C$H_2$ pip + 2H, C$H_2$N), 4.05 (m, 1H, CH$_2$C*H* endo), 4.25 (m, 4H, OC$H_2$C$H_2$O), 6.55 (m, 2H, Bzd H-6,8), 6.75 (m, 1H, Bzd H-7), 7.1–7.3 (m, 3H, arom), 11.1 (br, 1H, NH$^+$).

**1-(2,3-Dihydro-1,4-benzodioxin-5-yl)-4-[2-(5-methoxybenzocyclobutan-1-yl)ethyl]piperazine, hydrochloride (28):** eluted with $CH_2Cl_2$/AcOEt, 95:5; $^1$H NMR (DMSO-$d_6$) 2.15 (m, 2H, C$H_2$CH$_2$N0, 2.7 (dd, 1H, *H*CHCH endo), 3.0–3.6 (cluster of 12H, 1H, CH$_2$C*H* endo + 1H, HC*H*CH endo + 8H, C$H_2$ pip + 2H, CH$_2$C$H_2$N), 3.7 (s, 3H, OC$H_3$), 4.2 (m, 4H, OC$H_2$C$H_2$O), 6.5 (m, 2H, Bzd H-6,8), 6.7 (t, 1H, Bzd H-7), 6.75–7.0 (m, 3H, arom), 11.2 (br, 1H, NH$^+$).

**1-(2,3-Dihydro-1,4-benzodioxin-5-yl)-4-[2-(4,5-dimethoxybenzocyclobutan-1-yl)ethyl]piperazine, hydrochloride (29):** eluted with $CH_2Cl_2$/AcOEt, 95:5; $^1$H NMR (DMSO-

$d_6$) 2.15 (m, 2H, $CH_2CH_2N$), 2.7 (dd, 1H, $HCHCH$ endo), 3.0–3.7 (cluster of 12H, 1H, $CH_2CH$ endo + 1H, $HCHCH$ endo + 8H, $CH_2$ pip + 2H, $CH_2CH_2N$), 3.7 (2s, 6H, $OCH_3$), 4.25 (s, 4H, $OCH_2CH_2O$), 6.55 (m, 2H, Bzd H-6,8), 6.75 (t, 1H, Bzd H-7), 6.75 and 6.85 (2s, 2H, arom), 11.1 (br, 1H, $NH^+$).

**1-(2,3-Dihydro-1,4-benzodioxin-5-yl)-4-[2-(5,6-dimethoxyindan-1-yl)ethyl]piperazine, hydrochloride (30):** $^1H$ NMR ($CDCl_3$) 1.7 (m, 1H, $CH_2HCHCH$ endo), 2.15 (m, 1H, $HCHCH_2N$), 2.3 (m, 1H, $CH_2HCHCH$ endo), 2.5 (m, 1H, $HCHCH_2N$), 2.85 (m, 2H, $CH_2CH_2CH$ endo), 2.95–3.15 (m, 4H, $CH_2$ pip), 3.25 (m, 1H, $CH_2CH_2CH$ endo), 3.4–3.7 (cluster of 6H, 4H, $CH_2$ pip + 2H, $CH_2CH_2N$), 3.85 and 3.9 (2s, 6H, $OCH_3$), 4.3 (m, 4H, $OCH_2CH_2O$), 6.5 (d, 1H, Bzd H-8), 6.65 (d, 1H, Bzd H-6), 6.8 (m, 3H, 2H arom + 1H, Bzd H-7), 12.8 (br, 1H, $NH^+$).

**1-(3-Benzocyclobutan-1-ylpropyl)-1-(1,5-benzodioxepin-6-yl)piperazine, hydrochloride (33):** eluted with $CH_2Cl_2$; $^1H$ NMR (DMSO-$d_6$) 1.5–2.0 (m, 4H, $CH_2CH_2CH_2N$), 2.15 (m, 2H, $OCH_2CH_2CH_2O$), 2.75 (dd, 1H, $HCHCH$ endo), 3.0–3.6 (cluster of 12H, 1H, $HCHCH$ endo + 1H, $CH_2CH$ endo + 8H, $CH_2$ pip + 2H, $CH_2CH_2CH_2N$), 4.1 (m, 4H, $OCH_2CH_2CH_2O$), 6.65 (m, 2H, Bzd H-7,9), 6.85 (t, 1H, Bzd H-8), 7.1–7.3 (m, 4H, arom), 10.75 (br s, 1H, $NH^+$).

**4-(3-Benzocyclobutan-1-ylpropyl)-1-benzofuran-7-yl-piperazine, fumarate (36):** eluted with $CH_2Cl_2$/MeOH, 97:3; $^1H$ NMR (DMSO-$d_6$) 1.65 (m, 4H, $CH_2CH_2CH_2N$), 2.6–2.8 (cluster of 3H, 1H, $HCHCH$ endo + 2H, $CH_2CH_2CH_2N$), 2.9 (m, 4H, $CH_2$ pip), 3.2–3.4 (cluster of 5H, 4H, $CH_2$ pip + 1H, $HCHCH$ endo), 3.45 (m, 1H, $CH_2CH$ endo), 6.2 (br, 3H, $NH^+$, OH fum), 6.6 (s, 2H, $HC{=}CH$ fum), 6.75 (d, 1H, Bzf H-6), 6.9 (d, 1H, Bzd H-3), 7.0–7.3 (cluster of 6H, 4H, arom + 2H, Bzf H-4,5), 7.95 (d, 1H, Bzf H-2).

**Biological Methods. Binding Studies at 5-$HT_{1A}$ and 5-$HT_{1B}$ Receptors.**[10] Male Wistar rats (Iffa Credo, Illskirchen, France) were killed by decapitation. Brain structures (hippocampus for 5-$HT_{1A}$ and frontal cortex for 5-$HT_{1B}$) were rapidly dissected and kept frozen until use. On the day of experimentation, structures were weighed for a final concentration (wt/vol) of $^1/_{100}$ and $^1/_{40}$ for hippocampus and frontal cortex, respectively. Structures were then thawed and homogenized using a Polytron homogenizer (1 min, position 5) in 20 vol of the assay buffer (Tris-Base (50 mM, pH 7.7), containing pargylline (10 mM), $CaCl_2$ (4 mM), and ascorbic acid (0.1%). After a first centrifugation for 20 min at 25000$g$ at 4 °C (Sorvall RC5B, Du Pont de Nemours), the pellet was resuspended and incubated for 30 min at 37 °C. This was followed by a second centrifugation. The resulting pellet was then resuspended in the adjusted volume. Radioligand, nonspecific binding, incubation time, and temperature were as follows for 5-$HT_{1A}$: [$^3H$]-8-OH-DPAT at 0.4 nM, 5-HT at 10 mM, 30 min at 25 °C. 5-$HT_{1B}$: [$^3H$]-5-HT at 2.0 nM, 5-CT at 10 mM, 30 min at 25 °C. 5-$HT_{1B}$ binding was performed in the presence of 100 nM 8-OH-DPAT and 100 nM mesulergine to mask 5-$HT_{1A}$ and 5-$HT_{2A}$ sites, respectively. Reaction was stopped by a rapid filtration through Whatman GF/B filters presoaked in 0.1% poly(ethylenimine) using a Brandle cell harvester (Gaithersburg, MD) followed by two successive washings. Radioactivity retained on filters was then counted in a Packard Tricarb 1500 instrument using an Ultima Gold MV (Packard) as scintillator. Inhibitory concentration ($IC_{50}$) values were determined using procedure 5 (analysis of a regression line) of Tallarida and Murray, 1987. The p$K_i$ was calculated as $-\log[IC_{50}/(1 + [L]/K_d)]$ where [L] is the concentration of the hot ligands and $K_d$ is the apparent dissociation constant (derived from saturation experiments). Drugs were dissolved in dimethyl sulfoxide at $10^{-2}$ M. Radioligands were all purchased from Amersham.

**Binding Studies at $\alpha_1$-Adrenergic and Dopamine $D_2$ Receptors.** Brain structures (striatum for dopamine $D_2$ and frontal cortex for $\alpha_1$-adrenergic receptors) were rapidly dissected and kept frozen until use. On the day of experimentation, structures were weighed for a final concentration (wt/vol) of $^1/_{300}$ for striatum and $^1/_{80}$ for frontal cortex. Preparation of membranes was performed as described above, except that there was no incubation. Assay buffer, radioligand, nonspecific binding, incubation time, and temperature were for $D_2$: Tris-Base (50 mM, pH 7.4) containing $CaCl_2$ (4 mM), ascorbic acid (0.1%), KCl (5 mM), $MgCl_2$ (1 mM), and NaCl (120 mM), [$^3H$]spiperone (Amersham) at 0.2 nM, raclopride at 10 mM, 30 min at 37 °C. $\alpha_1$: Tris-Base (50 mM, pH 7.6) containing $CaCl_2$ (4 mM) and ascorbic acid (0.1%), [$^3H$]prazosin at 0.2 nM, phentolamine at 10 mM, 60 min at 25 °C. Ketanserin (100 nM) was added to mask 5-$HT_{2A}$ sites for determination of $D_2$ affinity. Filtration and calculation were performed as described above.

**Core Temperature.**[11] Male Wistar rats of 200–220 g, housed singly, were removed from home cages, and core (rectal) temperature was determined by use of a digital thermistoprobe. Then the rats were treated with either vehicle or the putative antagonist and returned to their home cages. Thirty minutes later, they were reinjected with either vehicle or 8-OH-DPAT (0.16 mg/kg) and returned to their cages for a further 30 min, and then core temperature was redetermined. The difference between basal and posttreatment values was calculated. The $ID_{50}$ (95% confidence limits) was calculated according to the method of Finney, 1964. The minimal effective dose (MED) for inhibition of the action of 8-OH-DPAT, as well as for induction of hypothermia by the antagonist alone, was determined relative to vehicle, employing ANOVA followed by Dunnett's test; the level of significance was set at $P < 0.05$. All drugs were dissolved in distilled water and given sc in a volume of 1.0 mL/kg.

**Palpebral Aperture (PA).**[12] Male Wistar rats of 200–220 g were injected with vehicle or the putative antagonist and returned to their home cages. Thirty minutes later, they were inspected for PA, which was scored as follows: 4, normal; 5, exophthalmia; 3, eyes three-fourth open; 2, eyes one-half open; 1, eyes one-fourth open; and 0, eyes completely shut. All drugs were dissolved in distilled water and given sc in a volume of 10.0 mL/kg. The $ED_{50}$ was based on the percentage of rats showing a score of ≤3; this was calculated according to the method of Litchfield and Wilcoxon (procedure 41 of Tallarida and Murray, 1987).

**Methylphenidate-Induced Gnawing.**[13] Male Wistar rats of 200–220 g were injected with the vehicle or the putative antagonist and then placed in a plastic observation chamber. Thirty minutes thereafter, they received an injection of methylphenidate (40.0 mg/kg, ip), and 30 min later, observations were commenced. The number of gnawing bouts emitted over 10 s (10 s of observation/1 min yielding a theoretical maximum of 10 bouts) was determined by an observer unaware of drug treatment. The dose of methylphenidate used yielded maximal gnawing in at least 99% of vehicle-treated rats. All drugs were dissolved in distilled water and given sc in a volume of 1.0 mL/kg except methylphenidate which was injected ip. The $ID_{50}$ (95% confidence limits) was calculated according to Finney, 1964. The slope of the dose–response curve was calculated according to procedure 6 of Tallarida and Murray, 1987.

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