4-Aryl-Substituted 2,5-Dimethoxyphenethylamines: Synthesis and Serotonin 5-HT_{2A} Receptor Affinities

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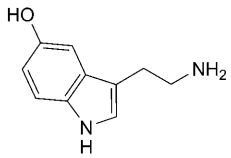
A series of novel ligands for the serotonin 5-$HT_{2A/C}$ receptor subtype bearing the 2-phenylethylamine pharmacophore was synthesized and assayed for its 5-HT_{2A} receptor binding affinity. As the 4′-aryl-substituted 2-(2,5-dimethoxyphenyl)ethylamines were previously unknown, an initial series of twelve compounds was chosen to obtain initial insight into their structure–activity relationships. The 4′-aryl moiety was introduced in moderate-to-high yield by a Pd-catalyzed *Suzuki* reaction of twelve arylboronic acids with *N*-Boc-protected 2-(2,5-dimethoxy-4-iodophenyl)ethylamine (**8**). *N*-Boc Deprotection then afforded the novel 2-phenylethylamines **5a**–**5l**. Additionally, biphenyl compound **6** lacking the 5′-MeO substituent was prepared, starting from 2-methoxy-4-hydroxybenzaldehyde. Except for **5l**, all of the compounds proved to be antagonists with generally low affinity at the rat 5-HT_{2A} receptor. Substituents are generally not well tolerated on the 4′-aryl moiety, except in the 4″-position. Indeed, the relatively high affinity of the 4″-butyl-, 4″-phenyl-, and 4′-naphthyl-substituted compounds **5i**, **5k**, and **5e**, respectively (K_i = 32, 33, and 41 nM, resp.), attests a rather remarkable tolerance for bulk in this location.

Introduction. – The serotonin 5-HT_2 receptor family was first identified in 1979 [1]. It is involved in regulation of the cardiovascular system and numerous central processes such as sleep, appetite, and sexual activity. A wide array of mental disorders including schizophrenia, depression, anxiety, migraine, and eating disorders also are believed to underlie abnormal neurotransmission within 5-HT_2 receptor-mediated pathways. Serotonin (5-HT; **1**) itself is the natural neurotransmitter agonist for these receptors, but it exhibits no selectivity, so it is of limited utility as a pharmacological tool.



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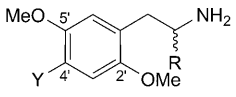

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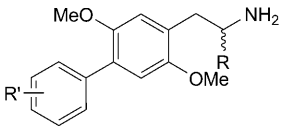

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The 5-HT_2 receptor family is comprised of three subpopulations, namely the 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} isoforms. To learn more about the role of each subtype,

there is a need for selective ligands paired with a selective functional activity. Numerous ligands with high affinity are known, many of which are simple phenethylamines (=2-phenylethylamines), although they lack receptor selectivity [2–6].

The well-studied 2-(4-bromo-2,5-dimethoxyphenyl)-1-methylethylamine (DOB; **2**, Y=Br, R=Me) binds with high affinity at the 5-HT_{2A} and 5-HT_{2C} (and 5-HT_{2B}) receptors, but has only low selectivity between them [2–6]. The reasons are assumed to lie in the high degree of sequence homology between the two receptor families in the transmembrane area where actual binding of the ligands occurs [7].

The phenethylamines represent attractive molecules for the development of pharmacological probes of 5-HT_2 family receptors, largely because they are synthetically easily accessible. Many of them also have been established as potent hallucinogens in man [8][9]. Thus, they have been extensively investigated for the past four decades in animal models and in humans.

Among these types of compounds, the most potent bear the general structure **2**, a phenethylamine with a 2′,4′,5′-substitution pattern, whereby the 2′- and 5′-position are ideally occupied by MeO groups and the 4′-position contains a lipophilic substituent (halogen, alkyl, alkylsulfanyl, *etc.*). The presence of an α-Me group (R=Me) has little effect on 5-$HT_{2A/C}$ affinity, and phenethylamines, therefore, have about the same affinity as their racemic α-methyl congeners (amphetamines) toward these binding sites [2][10–12]. Large differences in dosage and duration of action *in vivo* [13] observed in humans are thought to be partially due to increased metabolic stability [2][14] and increased hydrophobicity [15]. Nevertheless, the intrinsic activity at the receptor also seems to play an important role [13], where the α-Me compounds have increased intrinsic activity compared to the phenethylamines [12].

Usually, compounds of structure **2** bearing a small lipophilic substituent at the crucially important 4′-position possess agonist behavior (Y=halogen, Me, CF_3, *etc.*), whereas those having a large lipophilic substituent (Y=alkyl chain $\geq C_4$, 3-phenylpropyl, *etc.*) have antagonist activity [11], but to date the transition between these structures is not well-defined.

Most of the serotonin receptors, including the 5-HT_{2A} subtype, are G protein-coupled receptors (GPCR) [16][17]. Serotonin 5-HT_{2A} receptor models suggest two overlapping areas of accessibility for ligands ([18][19], reviewed in [20]). That is, agonists are believed to interact with transmembrane helices TM3 flanked by TM4, TM5, and TM6, whereas antagonists appear to interact with TM3, flanked by TM2, TM6, and TM7 (*Fig. 1*).

An immense number of phenylalkylamines of the general structure **2** (R=H or Me), which have a wide variety of substituents in the 4′-position (*e.g.*, Y=halo, alkyl, alkylsulfanyl, alkoxy, NO_2, CF_3, *etc.*) have been prepared and investigated by numerous researchers [8][13][21–29]. Nonetheless, (2,5-dimethoxyphenyl)alkylamines carrying a second phenyl moiety attached directly to C(4′) seem not to have been reported (general structure **3**). The idea for the introduction of a second phenyl moiety into unsubstituted 2-phenylethylamine was originally presented by *Benington et al.* in the late 1950s [30]. Among other 4′-substituted 2-phenylethylamines, one compound was tested on cat behavior, where it proved to be essentially inactive. In 1968, *Sam et al.* conducted studies to determine whether these compounds exhibited central nervous system activity and cardiovascular properties similar to unsubstituted

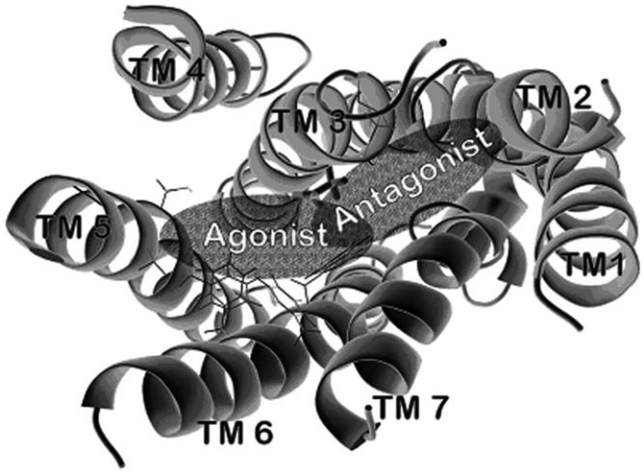


Fig. 1. *Illustration of overlapping but nonidentical binding sites for agonists and antagonists in the 5-HT$_{2A}$ receptor*

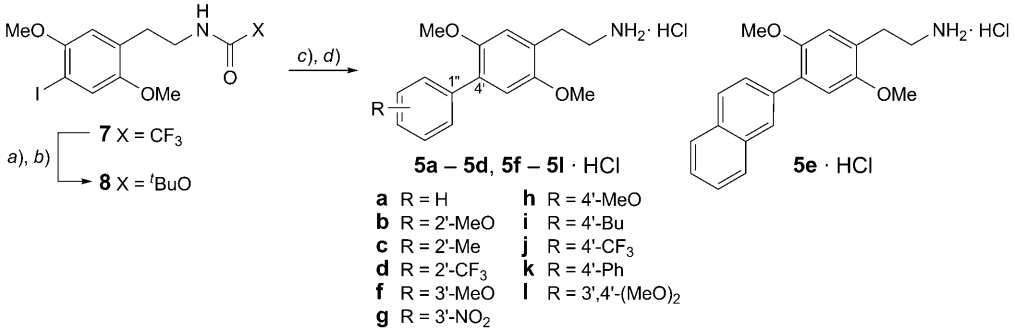
2-phenylethylamine [31]. The only 2-([1,1′-biphenyl]-4-yl)ethylamine investigated as a 5-HT receptor ligand was compound **4** (*cf. Fig. 2*), which is lacking a 5-MeO group [32].

Here, we describe the synthesis and the 5-HT$_{2A}$ receptor-binding properties of the 2-(biphenyl)ethylamines **5a**–**5l**. Furthermore, compound **6**, lacking the 5-MeO group but bearing an O-function on the appended aryl moiety, also was prepared and investigated.

Results and Discussion. – *Chemistry.* Initially, we attempted to convert *N*-trifluoroacetyl protected 2-(2,5-dimethoxy-4-iodophenyl)ethylamine (**7**) directly into the 2-(4-phenylphenyl)ethylamines **5a**–**5l** using a *Suzuki* protocol [33] (*Scheme 1*). Among the desired *N*-deprotected products, a substantial amount of **7** also was deiodinated (*ca.* 50%). Thus, because of the basic conditions during the *Suzuki* reaction, the base-labile CF_3CO protecting group had to be replaced by the (*tert*-butoxy)carbonyl (Boc) group. Starting from **7**, template **8** was obtained in 96% yield. Next, the *Suzuki* protocol [33] was applied using a series of arylboronic acids in an aqueous mixture of toluene, EtOH, 2M Na_2CO_3, and $Pd(PPh_3)_4$ catalyst (*Scheme 1*). These conditions led to the carbamate-protected biphenyls in modest to good yield (47–83%). Removal of Boc with anhydrous HCl/dioxane afforded the final amines **5a**–**5l** (2C-BI-1 to 2C-BI-12) in 75–100% yield, isolated as hydrochlorides.

The amine **6** was prepared according to the the method described by *Rangisetty et al.* [32] with some modifications of the reaction conditions. The introduction of the trifluoromethylsulfonyl (Tf) group into 4-hydroxy-2-methoxybenzaldehyde (**9**; *Scheme 2*) could be performed in high yield using 4-nitrophenyl triflate (easily prepared according to the method of *Zhu et al.* [34][35], but also commercially available; *e.g.*, *Aldrich*) in DMF in the presence of K_2CO_3 at room temperature. The reaction was complete within 90 min. The yield of **10** was 97%, and no chromatographic purification was necessary. When the introduction of the Tf group was performed using

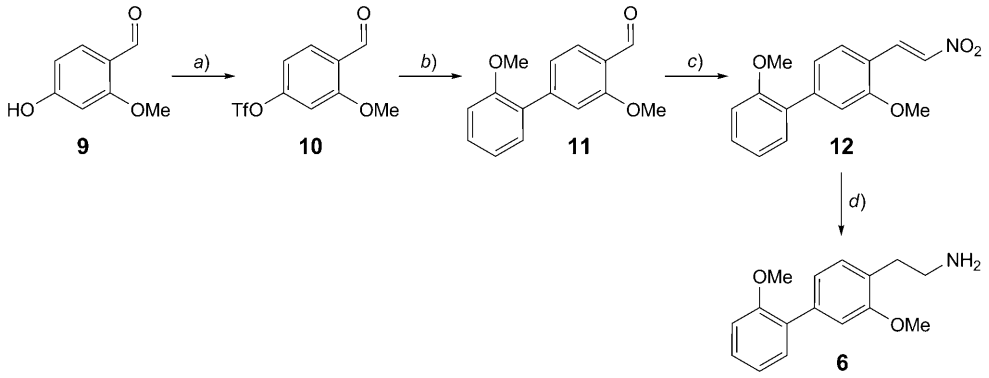
Scheme 1



a) 5M aq. NaOH, MeOH. *b*) $(Boc)_2O$, Et_3N, CH_2Cl_2. *c*) $ArB(OH)_2$, $Pd(PPh_3)_4$, toluene, EtOH, 2M aq. Na_2CO_3. *d*) HCl, dioxane.

Tf_2O in CH_2Cl_2/pyridine, the yield was only 47% [32]. The *Suzuki* protocol described above was applied to **10** and worked as well for the preparation of compound **11**. A *Henry* condensation using the catalyst system $BuNH_2$/AcOH [29] yielded the nitrostyrene **12**. Final reduction of **12** with AlH_3 in THF at 0° afforded amine **6** in 75% yield.

Scheme 2



a) 4-Nitrophenyl triflate (= trifluoromethylsulfonate), DMF, K_2CO_3. *b*) $ArB(OH)_2$, $Pd(PPh_3)_4$, toluene, EtOH, 2M aq. Na_2CO_3. *c*) $MeNO_2$, AcOH, $BuNH_2$. *d*) AlH_3, THF.

Receptor-Binding Studies. Except for **5l**, all of the compounds proved to be antagonists at the rat 5-HT_{2A} receptor (*Table*). Compound **5l** was found to be a weak partial agonist, with an EC_{50} value of 1.2 μM, and intrinsic activity of 50–75% in the inositol phosphate accumulation assay.

With respect to affinity, it is clear from the *Table* that substituents are generally not well-tolerated, except in the 4″-position of the second phenyl moiety. Indeed, the relatively high affinity of the Bu-, Ph-, and naphthalen-2-yl-substituted compounds **5i**, **5k**, and **5e**, respectively, indicates a rather remarkable tolerance for bulk in this

Table. K_i *Values for Displacement of [^{3}H]Ketanserin from Rat 5-HT$_{2A}$ Receptors Expressed in NIH 3T3 Cells*

Compound	Proposed name	R[a])	K_i [nM] (SEM)
5a	2C-BI-1	H	778 (75)
5b	2C-BI-2	2′′-MeO	5920 (1050)
5c	2C-BI-3	2′′-Me	1130 (190)
5d	2C-BI-4	2′′-CF_3	590 (110)
5e	2C-BI-5	–	41 (8)
5f	2C-BI-6	3′′-MeO	1490 (220)
5g	2C-BI-7	3′′-NO_2	450 (100)
5h	2C-BI-8	4′′-MeO	99 (10)
5i	2C-BI-9	4′′-Bu	32 (5)
5j	2C-BI-10	4′′-CF_3	171 (20)
5k	2C-BI-11	4′′-Ph	33 (7)
5l	2C-BI-12	3′′,4′′-$(MeO)_2$	87 (9)
6	–	–	5362 (645)

[a]) For structures of compounds **5**, see *Scheme 1*. For structure of compound **6**, see *Scheme 2*.

location. The 4′′-MeO and 3′′,4′′-$(MeO)_2$ compounds **5h** and **5l**, respectively, have only slightly lower affinity, whereas the 2′′- and 3′′-MeO compounds **5b** and **5f**, respectively, have markedly reduced affinity. The substituent in 4′′-position may have some beneficial effect in binding, when the comparison is made between the 4′′-MeO- and 3′′,4′′-$(MeO)_2$-substituted substrates. The 3′′-MeO compound **5f** has *ca.* 14-fold lower affinity for the receptor, whereas, when the 4′′-MeO group is added, the 3′′,4′′-$(MeO)_2$ compound **5l** has an affinity identical to the 4′′-MeO compound. Further, **5l** is the only compound with agonist activity. The electron-withdrawing CF_3 and NO_2 substituents appear better tolerated than MeO, especially in the 2′′- and 3′′-positions (compounds **5d** and **5g**, resp.).

One may argue that a simple 4′-phenyl substituent in 2-phenylethylamines is still not large enough to allow full interaction with an 'antagonistic binding site' in the 5-HT_{2A} receptor, and that its steric bulk exceeds a limited space in the agonistic binding site. As soon as a further substituent is introduced, (especially) in the *para*-position of the second arene moiety, antagonistic binding increases dramatically, a conclusion that completely agrees with the results of *Glennon* and co-workers [11][32]: *i.e.*, as soon as larger 4′-alkyl or 4′-arylalkyl substituents are introduced into 2-phenylethylamines, the compounds behave as antagonists.

From the *Table*, it can be seen that the *ortho*-substituted compounds **5b**–**5d** tend to have decreased affinities, although the slightly higher affinity for the CF_3 group, compared with a Me or MeO group, could possibly result from enhanced $\pi-\pi$ stacking properties as a result of the electron-withdrawing properties of the CF_3 moiety. The extent to which *ortho*-substituents produce steric repulsion that leads to a favorable conformation is unknown, and it cannot be determined how that might influence affinity. Additionally, there may be some multidimensional phenomena (*e.g.*, steric bulk *vs.* electronic properties) that make further data analysis difficult with this very limited set of compounds.

Until recently, it was thought that the 2′,5′-$(MeO)_2$ pattern was required for high affinity of phenethylamines at the serotonin 5-HT_{2A} receptor (reviewed in [11]). Although this pharmacophore may be necessary for agonist action, assumed to be the primary pharmacology of hallucinogenic phenethylamines [36][37], *Glennon* and co-workers [11][32] have shown that this substitution pattern is not required for high-affinity *antagonists* such as **13**–**15**. In the series of compounds lacking the 5′-MeO substituent, biphenyl compound **4** was investigated [32].

As illustrated in *Fig. 2*, attaching a second phenyl moiety directly to the phenethylamine pharmacophore (*e.g.*, removing the C_3 spacer in compound **14**) leads to a compound, **4**, that shows >300-fold decreased affinity at the serotonin 5-HT_{2A} receptor compared with **14** (K_i = 6720 and 18 nM, resp.). It has also been shown that removal of the 5′-MeO group can substantially alter 5-HT_{2A} receptor affinity, when the crucial 4′-substituent has a small molar refraction: compound **16** bearing a 4′-Br substituent ('5-desmethoxy-2C-B') had significantly reduced affinity (K_i = 1030 nM) compared to the parent compound 2C-B (**17**; K_i = 34 nM) [2].

Although only a small number of similar compounds that either possess or lack a 5′-MeO group are available for comparison (4′-Br, and Ph-C_1 to Ph-C_4 spacer), we initially speculated that, when the 4′-substituent is as small as Br, the 5′-MeO is required for high affinity and agonist activity, but when a large 4′-substituent such as 3-phenylpropyl is attached, the 5′-MeO or even both MeO groups are no longer required for high 5-HT_{2A} receptor affinity. The fact that such compounds are antagonists, however, suggests that they may be adopting a binding pose that is different from that of agonists.

Compound **6** was then prepared to investigate whether a MeO group attached to the second arene ring could mimic to any extent the 5′-MeO substituent in compounds such as **2** (*Fig. 3*). As shown by several researchers [3][6][38], the planarity of 4′-substituted 2-(2,5-dialkoxyphenyl)ethylamines and the orientation of the lone-pair electrons of the two O-atoms seem to be key factors for high agonist activity. The electron pairs of the O-atom in 2′-position of **6** will be directed in an orientation opposite to that of compound **2**, due to the repulsion of both aryl moieties. Thus, it was interesting to determine whether it would possess any affinity for the receptor.

Comparison of **6** with the closest homologue, **5b** indicates that removal of the 5′-MeO at the core structure has no effect on affinity (*Table*). Furthermore, compound **5b** and **6** have about the same binding affinity as **4** (K_i = 5920 and 5360 nM *vs.* 6720 nM [32]). It must be kept in mind, however, that the binding scheme shown in *Fig. 3* resulted from a consideration of agonist activity, and the present series of compounds are antagonists, where a similar scheme is not likely to apply.

Experimental Part

General. All compounds were commercially available and were used without further purification. All reactions were monitored by TLC (silica-gel plates F_{254}; standard UV lamps were used for detection). M.p.: *Büchi 535* apparatus: uncorrected. All compounds were dried under vacuum at 50–60°. ^{1}H- and ^{13}C-NMR spectra: *Bruker AM-300* spectrometer; 300 MHz; δ in ppm, J in Hz.

tert-*Butyl* N-*[2-(2,5-Dimethoxy-4-iodophenyl)ethyl]carbamate* (**8**). A soln. of 10.0 g (28.64 mmol) *N-[2-(2,5-dimethoxy-4-iodophenyl)ethyl]-2,2,2-trifluoroacetamide* (**7**) [10][13] in 500 ml of MeOH was treated for 2 h with 25 ml of 5M NaOH at 40° with stirring under N_2. Then, the MeOH was evaporated, and the residue was extracted 3× with CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and then

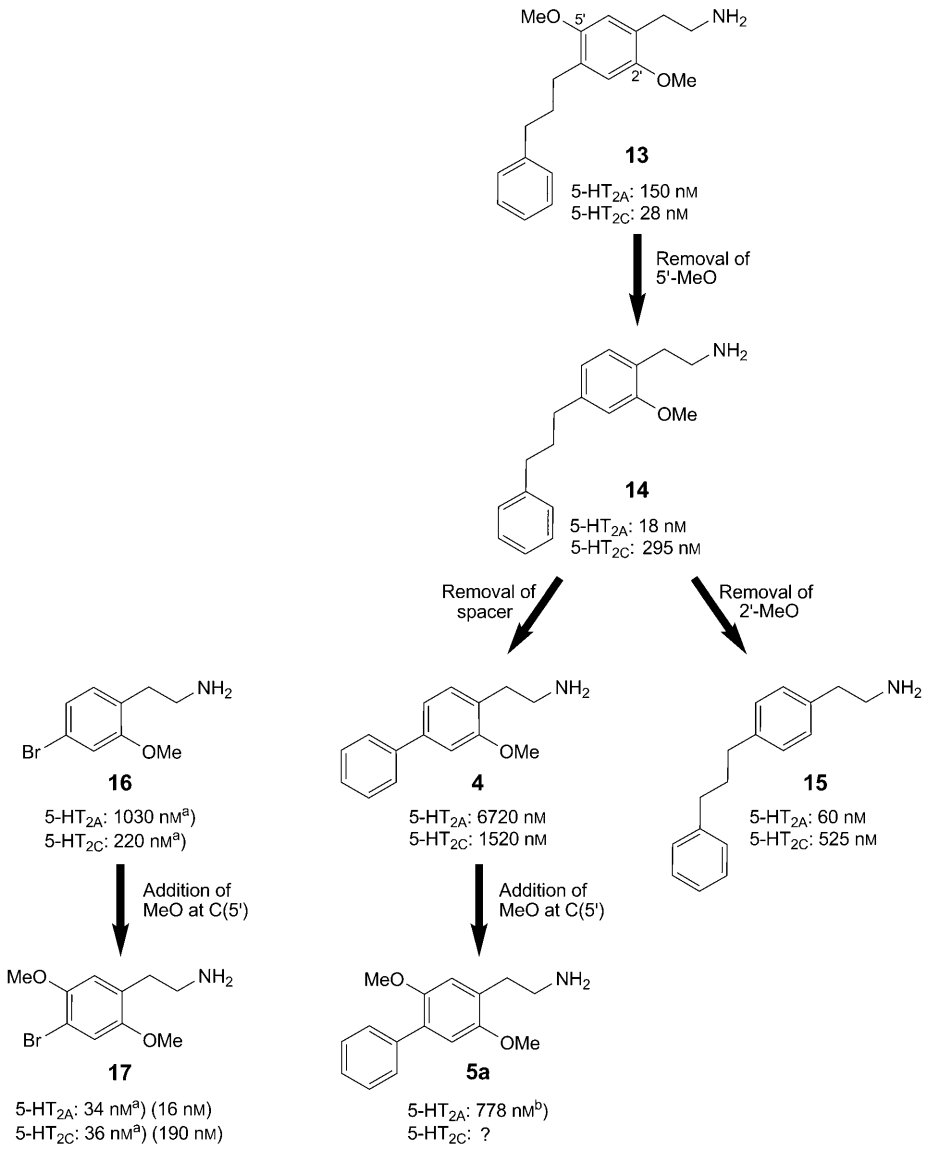


Fig. 2. *Influence of structural modifications upon binding affinities towards 5-HT$_2$ receptors* (unless otherwise indicated, K_i values were taken from [11] and [32]). [a]) Values taken from [2]. The values given in parentheses are more recent [11]; nevertheless, the prior K_i values were used for a consistent comparison. [b]) This work.

concentrated *in vacuo* to afford 7.39 g (97%) of the free base as a colorless oil, which appeared to absorb CO_2 and was converted to a salt as soon as possible, or stored under an inert atmosphere. Next, the free base was dissolved in 40 ml of anh. CH_2Cl_2, and NEt_3 (3.5 ml, 1.15 equiv.) was added, followed by the dropwise addition over 5 min of a soln. of 5.37 g (1.02 equiv.) of $(Boc)_2O$ in 20 ml of anh. CH_2Cl_2. After

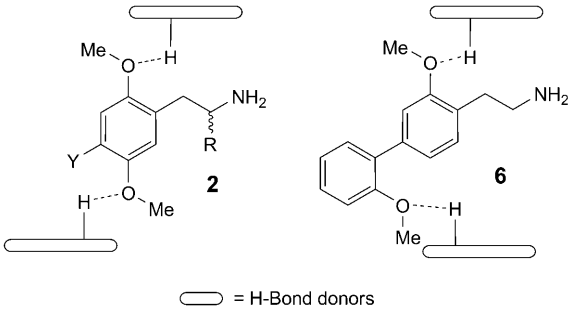


Fig. 3. *Schematic orientation of the O-atoms of substituted 2-phenylethylamines* **2** *on 5-HT$_2$ binding sites* (modified from [3] and [39]) *and a possible orientation of compound* **6**

stirring for 30 min, aq. 5% citric acid was added, and the mixture was stirred vigorously for 15 min. The layers were separated, and the aq. layer was further extracted once with CH_2Cl_2. The combined org. layers were washed 3× with aq. 5% citric acid, once with H_2O and brine, dried (Na_2SO_4), and evaporated *in vacuo*. The residual oil quickly solidified. Yield: 9.67 g (99%) of **8**. White solid. M.p. 107–108°. ^{1}H-NMR ($CDCl_3$): 1.43 (*s*, *t*-Bu); 2.78 (*t*, *J* = 7, ArCH_2); 3.29–3.38 (*m*, CH_2NH); 3.76 (*s*, MeO); 3.81 (*s*, MeO); 4.61 (br. *s*, NH); 6.63 (*s*, 1 arom. H); 7.21 (*s*, 1 arom. H).

Typical Procedure for the Suzuki Coupling (modified from [33]). Substrate **8** (300 mg, 0.75 mmol) and 0.87 mmol of the arylboronic acid were dissolved with occasional heating in a vial with a screw cap containing a mixture of 2 ml of toluene and 2 ml of EtOH. Freshly prepared aq. 2M Na_2CO_3 (3 ml) was added, and the mixture was degassed by bubbling Ar through the mixture for 20–30 s (a *Pasteur* pipet worked well). Then, 25 mg (0.03 equiv.) of a fresh batch of $Pd(PPh_3)_4$ were added quickly, and the gaseous void volume was again flushed with Ar for several seconds prior to closing the vial. The mixture was then heated to 75° in a preheated oil bath and stirred vigorously for 4 h. The mixture was cooled to r.t., diluted with 2 ml of H_2O, and extracted twice with AcOEt. The combined org. extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified over a short silica-gel column with either $CH_2Cl_2 \rightarrow CH_2Cl_2$/MeOH 95 : 5 or hexanes/AcOEt 9 : 1.

Typical Procedure for the Cleavage of the N-Boc Group. The *N*-Boc-protected amine was dissolved in 2.0 ml of anh. dioxane and treated with 1.0 ml of anh. 4M HCl in dioxane, stirring for 20 h under a N_2 atmosphere. The volatiles were then completely removed *in vacuo*, and the residual solid was finely powdered using a spatula and rinsed several times with anh. Et_2O. The Et_2O was carefully decanted using a pipette plugged with a small piece of cotton wool, and the residue was allowed to air dry.

N-*Boc-2-(2,5-Dimethoxy-4-phenylphenyl)ethylamine* (*N*-Boc-**5a**). 219 mg (81%). Beige solid. M.p. 132–133°. ^{1}H-NMR ($CDCl_3$): 1.44 (*s*, *t*-Bu); 2.84 (*t*, *J* = 7, ArCH_2); 3.35–3.43 (*m*, CH_2NH); 3.73 (*s*, MeO); 3.82 (*s*, MeO); 4.71 (br. *s*, NH); 6.79 (*s*, 1 arom. H); 6.83 (*s*, 1 arom. H); 7.28–7.56 (*m*, 5 arom. H).

2-(2,5-Dimethoxy-4-phenylphenyl)ethylamine Hydrochloride (**5a**·HCl; 2C-BI-1). From *N*-Boc-**5a**, 163 mg (91%) of **5a**·HCl. White crystals. M.p. 263.7°. ^{1}H-NMR ((D$_6$)DMSO): 2.86–2.95 (*m*, ArCH_2); 2.98–3.07 (*m*, CH_2NH$_3$); 3.72 (*s*, MeO); 3.81 (*s*, MeO); 6.92 (*s*, 1 arom. H); 6.99 (*s*, 1 arom. H); 7.28–7.54 (*m*, 5 arom. H); 8.07 (br. *s*, NH$_3$). ^{13}C-NMR ((D$_6$)DMSO): 151.7; 150.3; 138.5; 129.7; 129.4; 128.5; 127.3; 125.7; 115.3; 113.8; 56.7; 56.4; 28.4.

N-*Boc-2-[2,5-Dimethoxy-4-(2-methoxyphenyl)phenyl]ethylamine* (*N*-Boc-**5b**). 242 mg (83%). White solid. M.p. 94–95°. ^{1}H-NMR ($CDCl_3$): 1.42 (*s*, *t*-Bu); 2.83 (*t*, *J* = 7, ArCH_2); 3.35–3.42 (*m*, CH_2NH); 3.71 (*s*, MeO); 3.79 (*s*, MeO); 3.81 (*s*, MeO); 4.74 (br. *s*, NH); 6.79 (*s*, 2 arom. H); 6.92–7.05 (*m*, 2 arom. H); 7.22–7.37 (*m*, 2 arom. H).

2-[2,5-Dimethoxy-4-(2-methoxyphenyl)phenyl]ethylamine Hydrochloride (**5b**·HCl; 2C-BI-2). From *N*-Boc-**5b**, 176 mg (87%) of **5b**·HCl. White crystals. M.p. 203.9–204.7°. ^{1}H-NMR ((D$_6$)DMSO): 2.86–2.94 (*m*, ArCH_2); 2.97–3.08 (*m*, CH_2NH$_3$); 3.65 (*s*, MeO); 3.07 (*s*, MeO); 3.74 (*s*, MeO); 6.93–7.16 (*m*, 3

arom. H); 7.28–7.36 (*m*, 1 arom. H); 8.12 (br. *s*, NH_3). ^{13}C-NMR ((D_6)DMSO): 157.2; 151.2; 151.0; 131.5; 129.1; 127.7; 127.1; 125.3; 120.5; 114.7; 114.6; 111.8; 56.6; 56.4; 55.8; 28.5.

N-*Boc-2-[2,5-Dimethoxy-4-(2-methylphenyl)phenyl]ethylamine* (*N*-Boc-**5c**). 207 mg (74%). White solid. M.p. 105–106°. ^{1}H-NMR ($CDCl_3$): 1.44 (*s*, *t*-Bu); 2.14 (*s*, Ar*Me*); 2.84 (*t*, *J* = 7, ArCH_2); 3.34–3.44 (*m*, CH_2NH); 3.68 (*s*, MeO); 3.77 (*s*, MeO); 4.72 (br. *s*, NH); 6.65 (*s*, 1 arom. H); 6.76 (*s*, 1 arom. H); 7.14–7.27 (*m*, 4 arom. H).

2-[2,5-Dimethoxy-4-(2-methylphenyl)phenyl]ethylamine Hydrochloride (**5c**·HCl; 2C-BI-3). From *N*-Boc-**5c**, 153 mg (89%) of **5c**·HCl. White crystals. M.p. 216.2°. ^{1}H-NMR ((D_6)DMSO): 2.08 (*s*, Ar*Me*); 2.88–2.98 (*m*, ArCH_2); 2.99–3.09 (*m*, CH_2NH_3); 3.66 (*s*, MeO); 3.75 (*s*, MeO); 6.73 (*s*, 1 arom. H); 6.95 (*s*, 1 arom. H); 7.08–7.15 (*m*, 1 arom. H); 7.16–7.27 (*m*, 3 arom. H); 8.12 (br. *s*, NH_3). ^{13}C-NMR ((D_6)DMSO): 151.3; 150.4; 138.8; 136.6; 130.3; 129.9; 129.5; 127.6; 125.9; 125.4; 114.3; 114.1; 56.4; 56.3; 28.5; 20.2.

N-*Boc-2-{2,5-Dimethoxy-4-[2-(trifluoromethyl)phenyl]phenyl}ethylamine* (*N*-Boc-**5d**). 222 mg (70%). Viscous oil. ^{1}H-NMR ($CDCl_3$): 1.44 (*s*, *t*-Bu); 2.72–2.97 (*m*, ArCH_2); 3.35–3.43 (*m*, CH_2NH); 3.66 (*s*, MeO); 3.75 (*s*, MeO); 4.71 (br. *s*, NH); 6.66 (*s*, 1 arom. H); 6.74 (*s*, 1 arom. H); 7.31 (*d*, *J* = 7.5, 1 arom. H); 7.44 (*t*, *J* = 7.6, 1 arom. H); 7.54 (*t*, *J* = 7.3, 1 arom. H); 7.73 (*d*, *J* = 7.8, 1 arom. H).

2-{2,5-Dimethoxy-4-[2-(trifluoromethyl)phenyl]phenyl}ethylamine Hydrochloride (**5d**·HCl; 2C-BI-4). From *N*-Boc-**5d**, 172 mg (91%) of **5d**·HCl. White crystals. M.p. 198°. ^{1}H-NMR ((D_6)DMSO): 2.82–2.98 (*m*, ArCH_2); 2.98–3.11 (*m*, CH_2NH_3); 3.64 (*s*, MeO); 3.73 (*s*, MeO); 6.78 (*s*, 1 arom. H); 6.95 (*s*, 1 arom. H); 7.31 (*d*, *J* = 7.5, 1 arom. H); 7.58 (*t*, *J* = 7.6, 1 arom. H); 7.68 (*t*, *J* = 7.3, 1 arom. H); 7.79 (*d*, *J* = 7.8, 1 arom. H); 8.10 (br. *s*, NH_3). ^{13}C-NMR ((D_6)DMSO): 150.7; 150.6; 137.5; 132.9; 132.4; 128.4; 127.2; 126.3; 124.6 (*q*, *J* = 272); 113.9; 56.4; 56.3; 28.5.

N-*Boc-2-[2,5-Dimethoxy-4-(naphthalen-2-yl)phenyl]ethylamine* (*N*-Boc-**5e**). 230 mg (75%) as a beige solid. M.p. 117–118°. ^{1}H-NMR ($CDCl_3$): 1.43 (*s*, CMe_3); 2.87 (*t*, *J* = 7, ArCH_2); 3.34–3.44 (*m*, CH_2NH); 3.76 (*s*, MeO); 3.84 (*s*, MeO); 4.72 (br. *s*, NH); 6.82 (*s*, 1 arom. H); 6.94 (*s*, 1 arom. H); 7.42–7.52 (*m*, 2 arom. H); 7.68 (*d*, *J* = 8.5, 1 arom. H); 7.81–7.90 (*m*, 3 arom. H); 7.96 (*s*, 1 arom. H).

2-[2,5-Dimethoxy-4-(naphthalen-2-yl)phenyl]ethylamine Hydrochloride (**5e**·HCl; 2C-BI-5). From *N*-Boc-**5e**, 159 mg (82%) of **5e**·HCl. White crystals. M.p. 274.7°. ^{1}H-NMR ((D_6)DMSO): 2.90–2.99 (*m*, ArCH_2); 2.99–3.10 (*m*, CH_2NH_3); 3.75 (*s*, MeO); 3.84 (*s*, MeO); 7.04 (*s*, 1 arom. H); 7.06 (*s*, 1 arom. H); 7.48–7.58 (*m*, 2 arom. H); 7.69 (*dd*, *J* = 8.5, 1.7, 1 arom. H); 7.89–7.99 (*m*, 3 arom. H); 8.01 (*s*, 1 arom. H); 8.09 (br. *s*, NH_3). ^{13}C-NMR ((D_6)DMSO): 151.9; 150.6; 136.2; 133.4; 132.4; 129.3; 128.5; 128.3; 128.1; 127.9; 127.6; 126.5; 126.4; 125.9; 115.3; 114.0; 56.8; 56.5; 28.5.

N-*Boc-2-[2,5-Dimethoxy-4-(3-methoxyphenyl)phenyl]ethylamine* (*N*-Boc-**5f**). 154 mg (53%). Viscous oil. ^{1}H-NMR ($CDCl_3$): 1.42 (*s*, *t*-Bu); 2.83 (*t*, *J* = 7, ArCH_2); 3.34–3.43 (*m*, CH_2NH); 3.75 (*s*, MeO); 3.80 (*s*, MeO); 3.83 (*s*, MeO); 4.71 (br. *s*, NH); 6.76–6.91 (*m*, 3 arom. H); 7.07–7.14 (*m*, 2 arom. H); 7.33 (*t*, *J* = 8, 1 arom. H).

2-[2,5-Dimethoxy-4-(3-methoxyphenyl)phenyl]ethylamine Hydrochloride (**5f**·HCl; 2C-BI-6). From *N*-Boc-**5f**, 122 mg (95%) of **5f**·HCl. White crystals. M.p. 219.4°. ^{1}H-NMR ((D_6)DMSO): 2.86–2.95 (*m*, ArCH_2); 2.96–3.08 (*m*, CH_2NH_3); 3.72 (*s*, MeO); 3.78 (*s*, MeO); 3.81 (*s*, MeO); 6.88–6.94 (*m*, 2 arom. H); 6.99 (*s*, 1 arom. H); 7.01–7.09 (*m*, 2 arom. H); 7.32 (*t*, *J* = 7.9, 1 arom. H); 8.07 (br. *s*, NH_3). ^{13}C-NMR ((D_6)DMSO): 159.4; 151.7; 150.3; 139.9; 129.5; 129.2; 125.7; 122.1; 115.6; 115.3; 113.8; 112.6; 56.7; 56.4; 55.5; 28.4.

N-*Boc-2-[2,5-Dimethoxy-4-(3-nitrophenyl)phenyl]ethylamine* (*N*-Boc-**5g**). 143 mg (47%). Viscous oil. ^{1}H-NMR ($CDCl_3$): 1.42 (*s*, *t*-Bu); 2.85 (*t*, *J* = 7, ArCH_2); 3.35–3.45 (*m*, CH_2NH); 3.77 (*s*, MeO); 3.83 (*s*, MeO); 4.69 (br. *s*, NH); 6.83 (*s*, 2 arom. H); 7.55 (*t*, *J* = 8, 1 arom. H); 7.85 (*d*, *J* = 8, 1 arom. H); 8.19 (*d*, *J* = 8, 1 arom. H); 8.39 (*s*, 1 arom. H).

2-[2,5-Dimethoxy-4-(3-nitrophenyl)phenyl]ethylamine Hydrochloride (**5g**·HCl; 2C-BI-7). From *N*-Boc-**5g**, 101 mg (84%) of **5g**·HCl. White crystals. M.p. 220°. ^{1}H-NMR ((D_6)DMSO): 2.89–2.98 (*m*, ArCH_2); 2.98–3.10 (*m*, CH_2NH_3); 3.77 (*s*, MeO); 3.83 (*s*, MeO); 7.06 (*s*, 1 arom. H); 7.07 (*s*, 1 arom. H); 7.73 (*AB*, 1 arom. H); 7.99 (*AB*, 1 arom. H); 8.09 (br. *s*, NH_3); 8.20 (*AB*, 1 arom. H); 8.33 (*AB*, 1 arom. H). ^{13}C-NMR ((D_6)DMSO): 151.9; 150.2; 148.1; 139.9; 136.4; 130.1; 127.1; 126.6; 124.1; 122.2; 115.3; 113.7; 56.8; 56.5; 28.5.

N-*Boc-2-[2,5-Dimethoxy-4-(4-methoxyphenyl)phenyl]ethylamine* (*N*-Boc-**5h**). 231 mg (79%). Beige solid. M.p. 115–116°. ^{1}H-NMR ($CDCl_3$): 1.42 (*s*, *t*-Bu); 2.84 (*t*, *J* = 7, ArCH_2); 3.34–3.43 (*m*, CH_2NH); 3.73 (*s*, MeO); 3.81 (*s*, MeO); 3.84 (*s*, MeO); 4.72 (br. *s*, NH); 6.78 (*s*, 1 arom. H); 6.81 (*s*, 1 arom. H); 6.96 (*d*, *J* = 8.2, 2 arom. H); 7.46 (*d*, *J* = 8.2, 2 arom. H).

2-[2,5-Dimethoxy-4-(4-methoxyphenyl)phenyl]ethylamine Hydrochloride (**5h**·HCl; 2C-BI-8). From *N*-Boc-**5h**, 161 mg of (83%) of **5h**·HCl. White crystals. M.p. 251.7°. ^{1}H-NMR ((D_6)DMSO): 2.81–2.94 (*m*, ArCH_2); 2.95–3.06 (*m*, CH_2NH_3); 3.71 (*s*, MeO); 3.79 (*s*, MeO); 3.80 (*s*, MeO); 6.89 (*s*, 1 arom. H); 6.94–7.01 (*m*, 3 arom. H); 7.41–7.47 (*m*, 2 arom. H); 8.06 (br. *s*, NH_3). ^{13}C-NMR ((D_6)DMSO): 158.8; 151.7; 150.3; 130.3; 129.1; 125.0; 115.2; 113.9; 113.6; 56.7; 56.4; 55.6; 28.4.

N-*Boc-2-[2,5-Dimethoxy-4-(4-butylphenyl)phenyl]ethylamine* (*N*-Boc-**5i**). 179 mg (58%). Brown-beige solid. M.p. 80–81°. ^{1}H-NMR ($CDCl_3$): 0.94 (*t*, *J* = 7.3, *Me*CH_2); 1.35–1.51 (*m*, *t*-Bu, MeCH_2); 1.59–1.68 (*m*, EtCH_2); 2.63 (*t*, *J* = 7.6, ArCH_2Pr); 2.83 (*t*, *J* = 7, ArCH_2); 3.35–3.45 (*m*, CH_2NH); 3.73 (*s*, MeO); 3.80 (*s*, MeO); 4.72 (br. *s*, NH); 6.79 (*s*, 1 arom. H); 6.83 (*s*, 1 arom. H); 7.23 (*d*, *J* = 8.1, 2 arom. H); 7.43 (*d*, *J* = 8.1, 2 arom. H).

2-[2,5-Dimethoxy-4-(4-butylphenyl)phenyl]ethylamine Hydrochloride (**5i**·HCl; 2C-BI-9). From *N*-Boc-**5i**, 113 mg (75%) of **5i**·HCl. White crystals. M.p. 248.1°. ^{1}H-NMR ((D_6)DMSO): 0.92 (*t*, *J* = 7.3, *Me*CH_2); 1.27–1.41 (*m*, MeCH_2CH_2); 1.52–1.64 (*m*, EtCH_2); 2.60 (*t*, *J* = 7.6, ArCH_2Pr); 2.86–2.95 (*m*, ArCH_2); 2.97–3.07 (*m*, CH_2NH_3); 3.71 (*s*, MeO); 3.80 (*s*, MeO); 6.90 (*s*, 1 arom. H); 6.97 (*s*, 1 arom. H); 7.22 (*d*, *J* = 8.1, 2 arom. H); 7.41 (*d*, *J* = 8.1, 2 arom. H); 8.05 (br. *s*, NH_3). ^{13}C-NMR ((D_6)DMSO): 151.7; 150.3; 141.4; 135.8; 129.5; 129.3; 128.4; 125.3; 115.2; 113.7; 56.6; 56.4; 35.0; 33.6; 28.4; 22.3; 14.3.

N-*Boc-2-[2,5-Dimethoxy-4-[4-(trifluoromethyl)phenyl]phenyl]ethylamine* (*N*-Boc-**5j**). 209 mg (65%). White solid. M.p. 132–133°. ^{1}H-NMR ($CDCl_3$): 1.44 (*s*, *t*-Bu); 2.85 (*t*, *J* = 7, ArCH_2); 3.35–3.44 (*m*, CH_2NH); 3.77 (*s*, MeO); 3.82 (*s*, MeO); 4.70 (br. *s*, NH); 6.80 (*s*, 2 arom. H); 7.63 (*s*, 4 arom. H).

2-[2,5-Dimethoxy-4-[4-(trifluoromethyl)phenyl]phenyl]ethylamine Hydrochloride (**5j**·HCl; 2C-BI-10). From *N*-Boc-**5j**, 178 mg (100%) of **5j**·HCl. White crystals. M.p. 271°. ^{1}H-NMR ((D_6)DMSO): 2.89–2.97 (*m*, ArCH_2); 2.99–3.08 (*m*, CH_2NH_3); 3.75 (*s*, MeO); 3.82 (*s*, MeO); 6.99 (*s*, 1 arom. H); 7.05 (*s*, 1 arom. H); 7.70–7.80 (*m*, 4 arom. H); 8.12 (br. *s*, NH_3). ^{13}C-NMR ((D_6)DMSO): 151.8; 150.3; 142.7; 130.5; 128.0; 127.6; 126.8; 125.3; 125.3; 124.9 (*q*, *J* = 272); 115.3; 113.7; 56.7; 56.4; 28.4.

N-*Boc-2-[2,5-Dimethoxy-4-(4-phenylphenyl)phenyl]ethylamine* (*N*-Boc-**5k**). 203 mg (62%). Yellowish solid. M.p. 152–153°. ^{1}H-NMR ($CDCl_3$): 1.44 (*s*, *t*-Bu); 2.86 (*t*, *J* = 7, ArCH_2); 3.37–3.46 (*m*, CH_2NH); 3.78 (*s*, MeO); 3.83 (*s*, MeO); 4.72 (br. *s*, NH); 6.80 (*s*, 1 arom. H); 6.89 (*s*, 1 arom. H); 7.32–7.45 (*m*, 3 arom. H); 7.58–7.68 (*m*, 6 arom. H).

2-[2,5-Dimethoxy-4-(4-phenylphenyl)phenyl]ethylamine Hydrochloride (**5k**·HCl; 2C-BI-11). From *N*-Boc-**5k**, 159 mg (92%) of **5k**·HCl. White crystals. M.p. 275°. ^{1}H-NMR ((D_6)DMSO): 2.88–2.97 (*m*, ArCH_2); 2.98–3.10 (*m*, CH_2NH_3); 3.76 (*s*, MeO); 3.83 (*s*, MeO); 6.98 (*s*, 1 arom. H); 7.07 (*s*, 1 arom. H); 7.34–7.43 (*m*, 1 arom. H); 7.45–7.53 (*m*, 2 arom. H); 7.57–7.65 (*m*, 2 arom. H); 7.67–7.75 (*m*, 4 arom. H); 8.09 (br. *s*, NH_3). ^{13}C-NMR ((D_6)DMSO): 151.8; 150.4; 140.4; 139.1; 137.7; 130.2; 129.4; 128.8; 127.9; 127.1; 126.8; 125.8; 115.3; 113.7; 56.7; 56.4; 28.5.

N-*Boc-2-[2,5-Dimethoxy-4-(3,4-dimethoxyphenyl)phenyl]ethylamine* (*N*-Boc-**5l**). 157 mg (50%). Orange-beige solid. M.p. 98–99°. ^{1}H-NMR ($CDCl_3$): 1.42 (*s*, *t*-Bu); 2.82 (*t*, *J* = 7, ArCH_2); 3.34–3.43 (*m*, CH_2NH); 3.74 (*s*, MeO); 3.83 (*s*, MeO); 3.89 (*s*, MeO); 3.90 (*s*, MeO); 4.71 (br. *s*, NH); 6.79 (*s*, 1 arom. H); 6.82 (*s*, 1 arom. H); 6.94 (*d*, *J* = 8.1, 1 arom. H); 7.03–7.12 (*m*, 2 arom. H).

2-[2,5-Dimethoxy-4-(3,4-dimethoxyphenyl)phenyl]ethylamine Hydrochloride (**5l**·HCl; 2C-BI-12). From *N*-Boc-**5l**, 123 mg (92%) of **5l**·HCl. White crystals. M.p. 232°. ^{1}H-NMR ((D_6)DMSO): 2.82–2.93 (*m*, ArCH_2); 2.95–3.06 (*m*, CH_2NH_3); 3.72 (*s*, MeO); 3.77 (*s*, MeO); 3.78 (*s*, MeO); 3.81 (*s*, MeO); 6.89–7.08 (*m*, 5 arom. H); 8.05 (br. *s*, NH_3). ^{13}C-NMR ((D_6)DMSO): 151.7; 150.3; 148.6; 148.4; 131.1; 129.3; 125.1; 122.0; 115.3; 113.8; 113.7; 112.0; 56.7; 56.4; 56.1; 56.0; 28.4.

2-Methoxy-4-[(trifluoromethylsulfonyl)oxy]benzaldehyde (**10**; Adapted from [34][35]). A soln. of 3.04 g (20.0 mmol) *4-hydroxy-2-methoxybenzaldehyde* (**9**) in 100 ml of anh. DMF under N_2 was treated with 5.42 g (20.0 mmol) 4-nitrophenyl triflate [34] and 5.53 g (40.0 mmol) K_2CO_3 for 90 min while stirring at r.t. The mixture was diluted with 100 ml of H_2O and extracted with AcOEt (3×). The combined org. layers were washed with 0.5M NaOH (4×) until the yellow color disappeared, once with H_2O and brine, then dried (Na_2SO_4), filtered, and evaporated. The residual oil slowly crystallized upon

standing at r.t. Yield: 5.50 g (97%) **10**. Red-brown solid. M.p. 56–57°. ^{1}H-NMR ($CDCl_3$): 3.99 (*s*, MeO); 6.91 (*s*, 1 arom. H); 6.91 (*s*, 1 arom. H); 6.97 (*d*, *J* = 8.2, 1 arom. H); 7.94 (*d*, *J* = 8.2, 1 arom. H); 10.43 (*s*, CHO).

2-Methoxy-4-(2-methoxyphenyl)benzaldehyde (**11**). Applying the same *Suzuki* procedure described earlier, from 2.50 g (8.8 mmol) **10**, 1.55 g (10.2 mmol) 2-methoxyphenylboronic acid, and 250 mg (0.025 equiv.) $Pd(PPh_3)_4$ in toluene, EtOH and aq. 2M Na_2CO_3 (12 ml each) for 2 h, and after purifying the crude product over a dry flash column (silica gel; CH_2Cl_2), **11** (2.02 g, 95%) was obtained. White solid. M.p. 107–109°. ^{1}H-NMR ($CDCl_3$): 3.83 (*s*, MeO); 3.96 (*s*, MeO); 7.0–7.11 (*m*, 2 arom. H); 7.14–7.23 (*m*, 2 arom. H); 7.31–7.42 (*m*, 2 arom. H); 7.87 (*d*, *J* = 8.1, 1 arom. H); 10.49 (*s*, CHO).

2-Methoxy-4-(2-methoxyphenyl)-1-(2-nitroethenyl)benzene (**12**). A soln. of 1.0 g (4.12 mmol) of **11** in 3 ml of $MeNO_2$ was prepared by stirring with gentle heating. Then, 0.05 ml of $BuNH_2$ and 0.05 ml of AcOH were added, and the mixture was heated at 110° (preheated oil bath) for 35 min. The volatiles were then removed *in vacuo*. The residual oil slowly crystallized upon standing at r.t. Recrystallization from AcOEt/i-PrOH afforded 1.03 g (87%) of **12**. Yellow glistening crystals. M.p. 133–135°. ^{1}H-NMR ($CDCl_3$): 3.83 (*s*, MeO); 3.98 (*s*, MeO); 6.98–7.12 (*m*, 2 arom. H); 7.15–7.24 (*m*, 2 arom. H); 7.30–7.42 (*m*, 2 arom. H); 7.48 (*d*, *J* = 8, 1 arom. H); 7.92 (*d*, *J* = 14.5, ArCH=C*H*); 8.20 (*d*, *J* = 14.5, ArC*H*).

2-[2-Methoxy-4-(2-methoxyphenyl)phenyl]ethylamine Hydrochloride (**6**·HCl). To an ice-cooled suspension of 0.6 g of $LiAlH_4$ in 30 ml of anh. THF under N_2, 0.4 ml of conc. H_2SO_4 was added dropwise under vigorous stirring. Then, a soln. of 1.0 g (3.5 mmol) **12** in 15 ml of THF was added slowly. The cooling bath was removed, and the mixture was heated gently to reflux for 2 min with a heat gun. Then, the mixture was cooled again in an ice-bath, and excess hydride was quenched carefully by adding 2.5 ml of i-PrOH, followed by 2M aq. NaOH soln., keeping the thickening mixture stirred by addition of THF. After removing the salts by filtration, the solvents were removed *in vacuo* to afford the amine **6** as free base. It was dissolved in 50 ml of anh. Et_2O containing 0.5 ml of i-PrOH. The pH was lowered to *ca.* 5 by adding carefully 2M anh. HCl in Et_2O under vigorous stirring. The suspension was filtered off, and the filter cake was rinsed with Et_2O. Drying *in vacuo* afforded 0.771 g (75%) **6**·HCl. Beige solid. M.p. 125.1°. ^{1}H-NMR ((D_6)DMSO): 2.84–2.95 (*m*, ArCH_2); 2.95–3.06 (*m*, CH_2NH$_3$); 3.77 (*s*, MeO); 3.83 (*s*, MeO); 6.98–7.15 (*m*, 4 arom. H); 7.20 (*d*, *J* = 8, 1 arom. H); 7.27–7.39 (*m*, 2 arom. H); 8.04 (br. *s*, NH_3). ^{13}C-NMR ((D_6)DMSO): 157.20; 156.58; 138.75; 130.77; 130.13; 129.97; 129.31; 124.22; 123.75; 121.92; 121.18; 112.39; 112.24; 55.94; 55.84; 28.25.

Pharmacology. All compounds were assessed for their affinity at the cloned rat 5-HT$_{2A}$ receptor, using displacement of [^{3}H]ketanserin. In addition, functional potency and intrinsic activity were determined using the inositol phosphate accumulation assay [40].

Materials. [^{3}H]Ketanserin was obtained from *Perkin-Elmer Life and Analytical Sciences* (Boston, MA). Serotonin (5-HT) was obtained from *Sigma-Aldrich* (St. Louis, MO).

Cell Culture Methods. NIH-3T3 Cells stably expressing the rat 5-HT$_{2A}$ receptor (GF-6; 5500 fmol/mg) were the kind gift of Dr. *David Julius* (University of California, San Francisco, CA). Cells were maintained as described previously by *Braden et al.* [41]. All DMEM media contained 300 mg/ml G-418 (*Sigma-Aldrich*).

Radioligand Binding Assays. Membrane preparations and competition binding assays were performed as described in [4][5]. Competition binding assays were carried out using 0.5 nM [^{3}H]ketanserin in the presence of increasing concentrations of test compound (*ca.* 10 pM–10 mM). K_d Values and competition curves were calculated using *Prism* (Graphpad Software, San Diego, CA).

Inositol Phosphate Accumulation Assays. The ability of test compounds to stimulate radiolabeled inositol phosphate accumulation in NIH-3T3 cells stably expressing the rat 5-HT$_{2A}$ receptor was performed as described in [40]. Each assay plate was normalized to wells stimulated with H_2O (0%) and 10 μM serotonin (100%).

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