Articles

Influence of Amine Substituents on 5-HT2A versus 5-HT2C Binding of Phenylalkyl- and Indolylalkylamines

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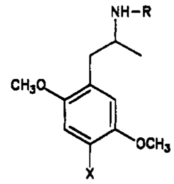
The effect of 15 different amine substituents on 5-HT2A and 5-HT2C serotonin receptor binding was investigated for two series of compounds (i.e., phenylalkylamine and indolylalkylamine derivatives). In general, amine substitution decreases receptor affinity; however, *N*-(4-bromobenzyl) substitution results in compounds that bind at 5-HT2A receptors with high affinity ($K_i < 1$ nM) and with >100-fold selectivity. Although parallel structural modifications in the two series result in parallel shifts in 5-HT2C binding, these same modifications alter 5-HT2A binding in a less consistent manner.

Due to their high degree of transmembrane sequence homology and similar second messenger coupling systems, 5-HT2 and 5-HT1C serotonin receptors have been recently renamed 5-HT2A and 5-HT2C receptors to acknowledge that they belong to the same receptor subfamily.[1,2] In addition, many ligands previously shown to bind at 5-HT2A receptors have now been found to bind with nearly comparable affinity at 5-HT2C receptors. For example, the prototypical 5-HT2A (partial) agonist DOB [i.e., 1-(4-bromo-2,5-dimethoxyphenyl)-2-aminopropane; 1] binds with nearly equal affinity at both populations of receptors, and its radioiodinated counterpart, [^{125}I]DOI (i.e. [^{125}I]-2), labels both sites.[3] Indeed, there is a significant correlation ($r > 0.9$) between 5-HT2A and 5-HT2C affinities (K_i values) and less than 10-fold selectivity, for a series of variously aromatic-substituted phenylethylamine derivatives.[4] All attempts to achieve selectivity for 5-HT2A versus 5-HT2C sites by variation of aromatic substituents have been unsuccessful. On the other hand, the effect of terminal amine substitution has not been examined in detail. Perhaps one reason modification of the terminal amine has been neglected is because early investigations demonstrated that *N,N*-dimethyl and *N*-monopropyl substitution of DOB (1) results in significant decreases in 5-HT2A receptor affinity.[5,6] The *N*-monopropyl analog of DOB (i.e., 3; $K_i > 3000$ nM), for example, binds at 5-HT2A sites with >50-fold lower affinity than DOB itself.[6] Although there exists about an 80% amino acid sequence homology between 5-HT2A and 5-HT2C receptors,[1,2] the possibility exists, given the appropriate terminal amine substituent, that this substituent may be able to take advantage of remote sequence differences and, hence, enhance affinity and perhaps introduce some degree of selectivity. Because a preliminary investigation showed that the *N*-(4-phenylbutyl) analog of DOB (i.e., 4; 5-HT2A K_i = 360 ± 50 nM) binds with higher affinity than *N*-monopropyl DOB (3), we undertook an examination of a series of N-substituted derivatives.



1 X = Br, R = H
2 X = I, R = H
3 X = Br, R = $-(CH_2)_2CH_3$
4 X = Br, R = $-(CH_2)_4-Ph$
5 X = Br, R = $-CH_3$
6 X = Br, R = $-CH_2-Ph$

A second goal of this work was to determine if parallel structural modification of phenylalkylamines and indolylalkylamines has parallel effects on receptor affinity. That is, recent attempts to model 5-HT2A and 5-HT2C receptors have used either phenylalkylamines or indolylalkylamines (or both) to explain or account for likely binding features of the models.[7-10] At this time, however, there is relatively little evidence that these two classes of agents bind at 5-HT2 receptors in a common manner (i.e., utilize common binding sites). Indeed, the only compelling reason to think that a common mode of binding is likely is because ergolines, which possess both types of structural components within their rigid framework, bind with high affinity at both populations of sites.[11] If, however, these two classes of agents share a common mode of binding, it should be possible to demonstrate comparable effects on receptor affinity by making identical structure changes in both series of agents.

Thus, the goal of the present investigation was 2-fold: (i) to determine if structural modification of the terminal amine substituents of DOB-related phenylalkylamines can influence receptor affinity and 5-HT2A versus 5-HT2C selectivity and (ii) to determine if the same terminal amine substituents have a parallel effect on a second series of agents, namely indolylalkylamines.

Chemistry

Compounds needed for this study are shown in Table 1. For the most part, the new compounds were prepared by functionalizing the terminal amines of 7 or 5-methoxytryptamine (23). Several different methods were employed. Most of the *N*-benzyl derivatives were prepared by acylation of the precursor amine with the appropriately

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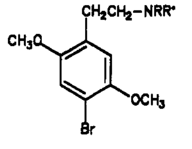
Table 1. Physicochemical Properties of Novel Phenylalkylamine and Indolylalkylamines



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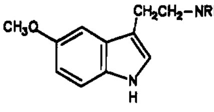

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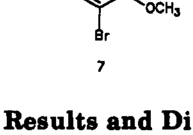
	R	R′	% yield	mp, °C	reaction solv[a]	M[b]	formula[c]
8	H	Me	10	174.5–176	$EtOH/Et_2O$	A[d]	$C_{11}H_{19}BrNO_2\cdot HCl$
9	Me	Me	64	186–188	2-PrOH	B	$C_{12}H_{19}BrNO_2\cdot HCl$
10	H	Et	60	224–225	2-PrOH	C	$C_{12}H_{19}BrNO_2\cdot HCl$
11	H	$(CH_2)_3Ph$	17	130–132	$EtOH/Et_2O$	D	$C_{20}H_{26}BrNO_2\cdot HCl$
13	H	CH_2Ph	50	202–204	$EtOH/Et_2O$	D	$C_{17}H_{20}BrNO_2\cdot HCl$
14	$-(CH_2)_5-$		18	225–227	$EtOH/Et_2O$	E	$C_{15}H_{22}BrNO_2\cdot HCl$
15	H	$CH_2Ph(4\text{-}F)$	75	218–220	$EtOH/H_2O$	C	$C_{17}H_{19}BrFNO_2\cdot C_2H_2O_4$
16	H	$CH_2Ph(4\text{-}Cl)$	77	212–214	$EtOH/H_2O$	C	$C_{17}H_{19}BrClNO_2\cdot C_2H_2O_4\cdot 0.75H_2O$
17	H	$CH_2Ph(4\text{-}Br)$	39	166–168	$EtOH/Et_2O$	C	$C_{17}H_{19}Br_2NO_2\cdot C_4H_4O_4$[e]$\cdot 0.75H_2O$
18	H	$CH_2Ph(4\text{-}I)$	79	233–235	$EtOH/H_2O$	C	$C_{17}H_{19}BrINO_2\cdot C_2H_2O_4$
19	H	$CH_2Ph(4\text{-}Me)$	71	224–225	$EtOH/H_2O$	C	$C_{18}H_{22}BrNO_2\cdot C_2H_2O_4\cdot H_2O$
20	H	$CH_2Ph(4\text{-}NH_2)$	55	164–166	EtOH	C	$C_{17}H_{21}BrN_2O_2\cdot C_2H_2O_4\cdot 0.5H_2O$[f]
21	H	$CH_2Ph(4\text{-}NO_2)$	66	204–206	$EtOH/H_2O$	C	$C_{17}H_{19}BrN_2O_4\cdot C_2H_2O_4$
22	H	$CH_2Ph(4\text{-}OMe)$	59	220–222	EtOH	C	$C_{18}H_{22}BrNO_3\cdot C_2H_2O_4$
27	H	$(CH_2)_3Ph$	68	149–151	Et_2O	A[g]	$C_{20}H_{24}N_2O\cdot C_2H_2O_4$
28	H	$(CH_2)_4Ph$	13	122–124	MeCN	F	$C_{21}H_{26}N_2O\cdot HCl$
30	$-(CH_2)_5-$		30	138–140	EtOH	F	$C_{15}H_{22}N_2O\cdot C_2H_2O_4\cdot H_2O$[h]
31	H	$CH_2Ph(4\text{-}F)$	66	210–212	Et_2O[i]	A[j]	$C_{18}H_{19}FN_2O\cdot C_2H_2O_4$
32	H	$CH_2Ph(4\text{-}Cl)$	43	203–205	Et_2O[i]	A[k]	$C_{18}H_{19}ClN_2O\cdot C_2H_2O_4$
33	H	$CH_2Ph(4\text{-}Br)$	67	208–210	Et_2O[i]	A[l]	$C_{18}H_{19}BrN_2O\cdot C_2H_2O_4$
34	H	$CH_2Ph(4\text{-}I)$	63	217–218	Et_2O[i]	A[m]	$C_{18}H_{19}IN_2O\cdot C_2H_2O_4$
35	H	$CH_2Ph(4\text{-}Me)$	42	158–159	2-PrOh	G	$C_{19}H_{22}N_2O\cdot HCl$
36	H	$CH_2Ph(4\text{-}NH_2)$	33	182–185	$MeOH/Et_2O$	H	$C_{18}H_{21}N_3O\cdot 1.75C_2H_2O_4$
37	H	$CH_2Ph(4\text{-}NO_2)$	41	230–232	MeOH	C	$C_{18}H_{19}N_3O_3\cdot HCl$
38	H	$CH_2Ph(4\text{-}OMe)$	40	183–184	95% EtOH	G	$C_{18}H_{22}N_2O_2\cdot HCl$

[a] Recrystalization solvent; Et_2O refers to anhydrous Et_2O and, unless otherwise noted, EtOH is absolute. [b] Method of preparation; see Experimental Section. [c] All new compounds analyzed correctly (±0.4%) for C, H, N, except where noted. [d] Intermediate amide: mp 78–82 °C (98% from Et_2O). [e] Fumarate salt. [f] C: calcd, 49.15; found, 49.63, N: calcd, 6.03; found, 5.61%. [g] Intermediate amide: colorless oil (83%). [h] N: calcd, 7.65; found, 8.08%. [i] Salt washed with anhydrous Et_2O. [j] Intermediate amide: mp 86–87 °C (78% from Et_2O). [k] Intermediate amide: mp 108–109 °C (58% from Et_2O/EtOH). [l] Intermediate amide: mp 113–115 °C (74% from Et_2O). [m] Intermediate amide: mp 159–164 °C (52% from Et_2O).

substituted benzoyl halide followed by reduction of the resulting amide with $LiAlH_4$ (method G; Table 1), diborane (method C), or alane (method A). Compounds **11**–**13** were prepared by acylation of the amines with an acid in the presence of NEt_3 and ethyl chloroformate, followed by reduction of the amide with diborane (method D). The *N*-(4-aminobenzyl)tryptamine **36** was obtained by catalytic reduction of the corresponding nitro derivative **37** (method H). Direct bromination of 2-(2,5-dimethoxyphenyl)-1-aminoethane provided **7**, which was used in many of the above reactions; Eschweiler–Clarke alkylation of **7** afforded **9** (method B). Compounds **28** and **30** were prepared by the Speeter–Anthony tryptamine synthesis (method F), and the piperidine derivative **14** was obtained by alkylation of piperidine with 2-(4-bromo-2,5-dimethoxyphenyl)-1-ethanol tosylate (method E). Compounds **23**–**26** and **29** were available from previous studies in our laboratories.



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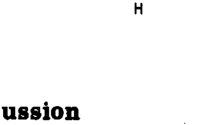

23 R=R'=H
24 R=H, R'=Me
25 R=R'=Me
26 R=H, R'=Et
29 R=H, R'=CH₂Ph

Results and Discussion

5-HT2A receptors in GF6 cells transfected with the human 5-HT2A gene were labeled with [^{3}H]ketanserin (identified as 5-HT2A(K) in Tables 2 and 3) or [^{125}I]DOI (identified as 5-HT2A(D) in Tables 2 and 3), and 5-HT2C receptors in J1 cells transfected with the rat 5-HT2C gene were labeled with [^{3}H]mesulergine.

Phenylalkylamine Analogues. 5-HT2A Binding. The aromatic bromo group of DOB (**1**) makes a significant contribution to binding, and its replacement by other substituents can modulate 5-HT2A affinity over a >1000-fold range.[12] Evidently, terminal amine substituents also influence affinity. Initially, we began by comparing the 5-HT2A and 5-HT2C affinities of DOB (**1**) (41 and 70 nM, respectively) with those of its *N*-monomethyl (K_i = 80 ± 10 and 100 ± 10 nM, respectively; **5**) and *N*-benzyl derivative **6** (10 ± 2 and 440 ± 65 nM, respectively). Interestingly, **6** binds at [^{3}H]ketanserin-labeled 5-HT2A sites with an affinity comparable to that of DOB (**1**) and with an affinity greater than that of *N*-monomethyl DOB (**5**), suggesting that the benzyl phenyl group makes a positive contribution to binding. Furthermore, whereas DOB displayed only 2-fold selectively, **6** showed 44-fold selectivity for 5-HT2A versus 5-HT2C sites. This selectivity ratio was higher than any we had previously noted for phenylalkylamine derivatives; thus, we were encouraged to continue this investigation.

Because the presence of the α-methyl group of DOB (**1**) makes little to no contribution to 5-HT2A or 5-HT2C binding,[4] the project was continued using analogs of α-desmethyl DOB (**7**) in order to avoid evaluation of pairs of optical isomers. Furthermore, because the use of [^{125}I]-DOI gives comparable results regardless of whether the ligands are agonists or antagonists (that is, [^{125}I]DOI labels the agonist high-affinity state of 5-HT2A receptors whereas

Table 2. 5-HT2A and 5-HT2C Binding Data for the Phenylalkylamine Derivatives

	receptor affinity, K_i, nM (±SEM)			receptor selectivity^c vs	
	5-HT2C	5-HT2A(K)^a	5-HT2A(D)^b	5-HT2A(K)	5-HT2C
7^b	36	34	1.0	34	36
8	100(±23)	380(±140)	2.9(±0.3)	130	34
9	480(±100)	420(±90)	16(±1)	26	30
10	1,930(±210)	330(±20)	40(±8)	8	48
11	310(±2)	84(±1)	23(±6)	4	13
12	695(±60)	100(±16)	27(±4)	4	26
13	90(±5)	16(±8)	0.3(±0.06)	53	300
14	2530(±220)	895(±130)	154(±10)	6	16
15	360(±15)	30(±5)	3.4(±1.3)	7	80
16	715(±25)	110(±20)	15(±2)	7	48
17	48(±3)	1.6(±0.3)	0.4(±0.1)	4	120
18	165(±40)	22(±1)	0.4(±0.2)	55	410
19	225(±15)	23(±7)	14(±2)	2	16
20	1020(±125)	50(±12)	16(±7)	3	64
21	1220(±125)	290(±60)	58(±18)	5	21
22	215(±15)	16(±1)	13(±7)	1	17

[a] [^{3}H]Ketanserin-labeled 5-HT2A receptors. [b] [^{125}I]DOI-labeled 5-HT2A receptors. [c] Receptor selectivity for binding at [^{125}I]DOI-labeled receptors versus [^{3}H]ketanserin-labeled receptors (i.e., 5-HT2A(K) K_i + 5-HT2A(D) K_i) or versus 5-HT2C receptors (i.e., 5-HT2C K_i + 5-HT2A(D) K_i). [d] K_i values were previously reported.[14]

[^{3}H]ketanserin labels both the high- and low-affinity state), and whereas agonists bind with lower affinity at [^{3}H]ketanserin-labeled sites than at [^{125}I]DOI-labeled sites, it has been suggested that use of [^{125}I]DOI gives more reliable structure–affinity data when the intrinsic activity of the ligands is unknown.[13] Thus, we continued by examining additional N-substituted α-desmethyl DOB analogs at 5-HT2C, [^{3}H]ketanserin-labeled 5-HT2A, and [^{125}I]DOI-labeled 5-HT2A sites. Table 2 provides binding data for a series of α-desmethyl DOB analogs; K_i values spanned a broad range. Examining affinities for [^{125}I]DOI-labeled 5-HT2A sites makes it is apparent that N-monomethylation (**8**; K_i = 2.9 nM), N,N-dimethylation (**9**; K_i = 16 nM), and N-monoethylation (**10**; K_i = 40 nM) result in decreased affinity. The *N*-(3-phenylpropyl) and *N*-(4-phenylbutyl) derivatives **11** and **12** (K_i = 23 and 27 nM, respectively) also bind with reduced affinity. Elaboration of the dimethyl groups of **9** into a piperidine ring (i.e., **14** K_i = 154 nM) further reduces affinity by 1 order of magnitude. However, as was noted above for DOB (**1**) and its *N*-benzyl derivative, the *N*-benzyl analog **13** (K_i = 0.3 nM) binds with several times the affinity of α-desmethyl DOB (**7**) and with 10 times the affinity of the *N*-monomethyl derivative **8**. Comparing the affinities of eight para-substituted *N*-benzyl derivatives shows that most substituents reduce affinity by 10–100-fold relative to **13**. The 4-bromo and 4-iodo derivatives **17** and **18**, however, retain the affinity of **13**. It is rather interesting to note that although the bromo and iodo derivatives **17** and **18** bind with comparable affinity, an affinity similar to that of **13**, the 4-chloro derivative **16** binds with nearly 50-fold lower affinity, an even lower affinity than with the 4-fluoro analog **15**. A second sample of **16** was prepared and submitted for binding, and the new K_i value was similar to the original value.

5-HT2C Binding. α-Desmethyl DOB (**7**)[14] displays 36-fold selectivity for 5-HT2A versus 5-HT2C sites but is, nonetheless, the highest-affinity phenylethylamine in this study. N-Alkylation reduces the affinity of **7** by at least severalfold. However, unlike what was observed for 5-HT2A binding, N-benzylation reduces, rather than increases, affinity by about 3-fold. Consequently, the benzyl derivative **13** displays 300-fold selectivity for 5-HT2A versus 5-HT2C sites.

Table 3. 5-HT2A and 5-HT2C Binding Data for Indolylalkylamines

	receptor affinity, K_i, nM (±SEM)			receptor selectivity^c vs	
	5-HT2C	5-HT2A(K)^a	5-HT2A(D)^b	5-HT2A(K)	5-HT2C
23	500(±50)	300(±20)	4.8(±1)	63	104
24	840(±150)	450(±20)	4.1(±0.9)	110	205
25	960(±180)	620(±40)	15(±2)	41	65
26	2675(±470)	930(±145)	7.2(±0.3)	130	510
27	165(±13)	50(±4)	10(±4)	5	16
28	1500(±35)	22(±1)	13(±3)	2	115
29	370(±40)	55(±5)	5.3(±0.7)	10	70
30	>10000	160(±35)	230(±30)	1	>40
31	3530(±1160)	480(±20)	40(±15)	10	88
32	4390(±330)	565(±75)	105(±10)	5	42
33	100(±10)	5.2(±0.6)	0.1(±0.01)	52	1000
34	1770(±20)	400(±25)	120(±30)	3	15
35	1225(±30)	110(±20)	30(±6)	4	40
36	6700(±220)	475(±95)	105(±35)	5	64
37	9970(±3000)	4260(±50)	140(±6)	30	70
38	1180(±25)	100(±15)	16(±2)	6	74

[a] [^{3}H]Ketanserinhlabeled 5-HT2A receptors. [b] [^{125}I]DOI-labeled 5-HT2A receptors. [c] Receptor selectivity for binding at [^{125}I]DOI-labeled receptors versus [^{3}H]ketanserin labeled receptors (i.e., 5-HT2A(K) K_i + 5-HT2A(D) K_i) or versus 5-HT2C receptors (i.e., 5-HT2C K_i + 5-HT2A(D) K_i).

Examination of the para-substituted benzyl derivatives shows that with one exception they all bind at 5-HT2C sites with lower affinity than the parent unsubstituted **13**. The 4-bromo derivative **17** binds with about twice the affinity of **13**. Nevertheless, the bromo- and iodobenzyl derivatives **17** and **18** still retain significant selectivity (120- and 410-fold, respectively) for 5-HT2A versus 5-HT2C sites.

[^{3}H]Ketanserin-Labeled 5-HT2A Binding. At this time, it is not known if **7–22** are 5-HT2A agonists, partial agonists, or antagonists. In the absence of such information, use of [^{125}I]DOI as radioligand should provide the most reliable 5-HT2A binding data. Nevertheless, even with the use of [^{3}H]ketanserin as radioligand it is evident that the *N*-benzyl derivative **13** and the *p*-bromobenzyl and *p*-iodobenzyl derivatives **17** and **18**, respectively, bind at 5-HT2A sites with significant affinity.

It has been suggested that a ratio of [^{3}H]ketanserin versus [^{125}I]DOI K_i values provides a rough approximation of agonist versus antagonist activity.[13] That is, compounds that bind with comparable affinity at [^{3}H]ketanserin-labeled and [^{125}I]DOI-labeled 5-HT2A sites have been demonstrated to be 5-HT2A antagonists, whereas agonists generally display 50- to >100-fold higher affinity for [^{125}I]-DOI-labeled versus [^{3}H]ketanserin-labeled 5-HT2A sites. The benzyl derivative **13** binds with 53-fold higher affinity and the *p*-iodobenzyl derivative **18** with 55-fold higher affinity, at [^{125}I]DOI-labeled relative to [^{3}H]ketanserin-labeled sites (Table 2). Interestingly the *p*-bromobenzyl derivative **17** displays only a 4-fold selectivity. The functional activity of some of these agents will need to be examined in the future.

Indolylalkylamine Analogues. 5-HT2A Binding. The same general trends described above for the phenylalkylamines were also noted with the indolylalkylamines (Table 3). That is, with respect to binding at [^{125}I]DOI-labeled 5-HT2A sites, small *N*-alkyl groups are tolerated but do not result in enhanced affinity, elaboration of the *N,N*-dimethyl groups of **25** to the piperidine derivative **30** results in decreased affinity, and the *N*-benzyl derivative **29** retains the affinity of the primary amine **23**. Most of the substituted *N*-benzyl derivatives (i.e. **31**, **32**, **34–38**), as was the case in the phenylalkylamine series, bind with lower affinity than the aromatic-unsubstituted parent *N*-benzyl derivative **29**. Again, however, the *N*-(4-bromobenzyl) derivative (i.e., **33**) binds with high affinity (**33**; K_i = 0.1 nM, Table 3). Interestingly, however, the corresponding iodo derivative **34** does not share the high affinity of the bromo compound **33**, as was the case with the phenylalkylamines **17** and **18**, but binds with an affinity similar to that of the chloro analogue **32**. These results may represent subtle differences in the manner in which these agents interact at 5-HT2A receptors.

5-HT2C Binding. Again, parallel trends are noted for the indolylakylamines versus the phenylalkylamines. Furthermore, as was the case in the phenylalkylamine series, the *N*-(4-bromobenzyl) derivative **33** is one of the few agents that retains the 5-HT2C affinity of the parent primary amine **23**. Nevertheless, **33** displays significant (1000-fold) selectivity for 5-HT2A versus 5-HT2C receptors. In contrast, the iodo derivative **34** (15-fold selectivity) is not nearly as 5-HT2A-selective as its phenylakylamine counterpart **18** (410-fold selectivity).

[^{3}H]Ketanserin-Labeled 5-HT2A Binding. Even with the use of [^{3}H]ketanserin as radioligand, it is still apparent that the bromo derivative **33** binds with high affinity (K_i = 5.2 nM) at 5-HT2A sites. Consistent with the results obtained using [^{125}I]DOI as radioligand, the iodo derivative **34** binds with low affinity (K_i = 400 nM). Furthermore, whereas the binding data in Table 2 suggest that the iodo phenylalkylamine **18** may behave as an agonist and the bromo phenylalkylamine **17** as an antagonist, the situation is reversed in the indolylalkylamine series. That is, with a 52-fold difference, the bromo indolylalkylamine **33** is suggested to possess agonist character, whereas the iodo derivative **34**, with only a 3-fold difference, may be an antagonist.

Binding Similarities. Even though certain agents display selectivity for 5-HT2A receptors, there still exists a significant overall correlation (r = 0.863, n = 15) between the affinities (pK_i values) of the indolylalkylamine derivatives **23**–**28**[15] at [^{125}I]DOI-labeled 5-HT2A receptors and 5-HT2C receptors. A similar correlation (r = 0.857, n = 16) exists for the phenylalkylamines **7**–**22**. These results support previous contentions that the binding of 5-HT2A ligands generally parallels their 5-HT2C affinities.

Do parallel amine alterations have similar consequences for the two series of compounds? With regard to 5-HT2A binding, this does not seem to be the case (r = 0.536, n = 16). Inspection of Figure 1 reveals that parallel trends may exist but that some compounds, notably some of the substituted *N*-benzyl derivatives of the phenylalkylamine series (e.g. **15**, **16**, **18**, **20**), bind at 5-HT2A receptors with higher affinity than their indolylalkylamine counterparts. Thus, although the overall correlation is rather poor, it cannot be reliably argued that binding similarities are altogether absent.

With regard to 5-HT2C binding, parallel structural changes apparently result in parallel shifts in affinity as reflected by the correlation (r = 0.850) that exits between the affinities of the 15 pairs of compounds.

Conclusions

We have previously reported that variously aryl-substituted phenylalkylamines bind with <10-fold selectivity for 5-HT2A versus 5-HT2C receptors when [^{3}H]-ketanserin is used as the radioligand to label 5-HT2A sites.[4] This is true, in general, for the compounds in the present investigation as well. However, a more realistic picture emerges when [^{125}I]DOI is used as radioligand. The phenylalkylamines **7**–**22** bind with 13–410-fold selectivity for 5-HT2A versus 5-HT2C receptors. Likewise, in the indolylalkylamine series **23**–**38**, 5-HT2A selectivity ranges from 15- to 1000-fold (Tables 2 and 3). None of the agents display selectivity for 5-HT2C receptors.

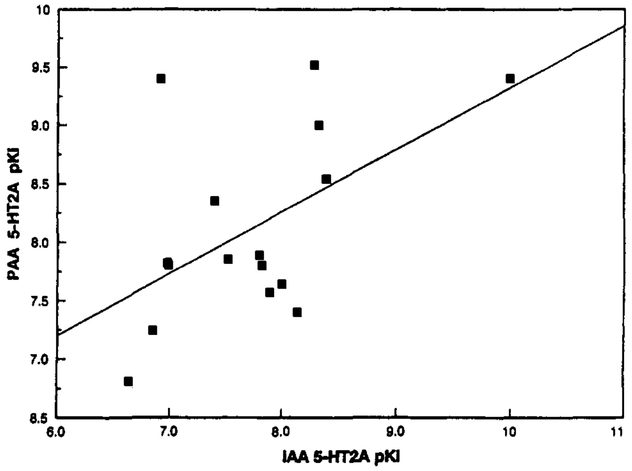

Figure 1. Relationship between [^{125}I]DOI-labeled 5-HT2A receptor affinities (pK_i values) for N-substituted phenylalkylamines and their corresponding indolylalkylamines.

In general, amine substitution is not beneficial for 5-HT2A binding. However, exceptions exist. In both series of compounds, *N*-benzyl substitution is tolerated; in addition, *N*-(4-bromobenzyl) substitution results in compounds (i.e., **17** and **33**) that bind at 5-HT2A receptors with K_i values of <1 nM. Furthermore, these compounds bind with >100-fold selectivity for 5-HT2A versus 5-HT2C receptors.

With respect to 5-HT2C binding, parallel structural changes on the terminal amine result in parallel changes in affinity, suggesting similar modes of binding for the two series of compounds. Results with 5-HT2A binding are less clear. Although there is a poor correlation between all K_i values for the two series, Figure 1 suggests a tendency for parallel structural modification to result in parallel shifts in affinity for many of the compounds examined. Several compounds tend to decrease the significance of this correlation (i.e. appear to be outliers). These include the halo-substituted benzyl derivatives. It would seem that there are some subtle differences in the manner in which the halo derivatives bind at 5-HT2A receptors. These differences are not only noted between the two series, but even within a series. For example, the bromo and iodo derivatives **17** and **18** bind with significantly higher affinity than the chloro derivative **16**. In the indolylalkylamine series, the bromo derivative **33** again binds with higher affinity than the chloro derivative **32**; however, in this series, the chloro and iodo derivatives (**32** and **34**, respectively) bind with comparable affinity. From a binding perspective, the bromobenzyl substituent may constitute an optimal binding feature which can be mimicked in the phenylalkylamine series, but not in the indolylalkylamine series, by the corresponding iodobenzyl substituent. In light of the present results, more detailed investigations of benzyl-substituted derivatives, including functional assays, are warranted.

Experimental Section

Synthesis. Melting points, determined with a Thomas-Hoover melting point apparatus, are uncorrected. Proton magnetic resonance spectra were obtained with a JEOL FX90Q spectrometer and GE QE-300 spectrometer with tetramethylsilane as an internal standard. Infrared spectra were recorded on a Nicolet 5ZDX FT-IR. Elemental analysis was performed by Atlantic Microlab, and determined values are within 0.4% of the theoretical values. Flash chromatography was performed on silica gel (Merck, grade 60, 230–400 mesh, 60 Å) using 95:5 mixture of methylene chloride (CH_2Cl_2) and (MeOH) as the eluent. Experimentals below illustrate the methods (methods A-H) referred to in Table 1. Compounds **26**[17] and **29**[18] were previously synthesized in our laboratories according to reported methods.

3-[2-(*N*-(4-Bromobenzyl)amino)ethyl)]-5-methoxyindole Oxalate (33). Method A. A solution of 4-bromobenzoyl chloride (0.57 g, 2.6 mmol) in dry THF (5 mL) was added in a dropwise manner to a stirred solution of 5-methoxytryptamine (0.5 g, 2.6 mmol) and Et_3N (0.52 g, 5.2 mmol) in THF (15 mL) at 0 °C. The reaction mixture was allowed to stir at room temperature overnight; the solid material was removed by filtration and the filtrate was evaporated to dryness under reduced pressure. A $CHCl_3$ solution of the oily residue was washed successively with 5% HCl (15 mL) and 5% Na_2CO_3 (100 mL) solutions and H_2O (50 mL). The $CHCl_3$ portion was dried ($MgSO_4$) and the solvent was removed under reduced pressure to afford 0.73 g (74%) of the amide intermediate as a white solid after recrystallization from Et_2O: mp 113–115 °C. AlH_3 was prepared by the careful addition of $AlCl_3$ (0.23 g, 1.7 mmol) to a suspension of $LiAlH_4$ (0.22 g, 5.8 mmol) in anhydrous Et_2O (15 mL) at 0 °C under a N_2 atmosphere. The suspension was stirred for 30 min at room temperature, then a solution of the above amide (0.37 g, 1 mmol) in Et_2O (10 mL) was added in a dropwise manner. The reaction mixture was allowed to stir for 5 h at room temperature. Excess AlH_3 was decomposed by the addition of crushed ice (1 g) and 20% NaOH solution (2 mL) at 0 °C. The mixture was filtered and the organic portion of the filtrate was washed with H_2O (3 × 15 mL) and dried ($MgSO_4$). The Et_2O solution of amine was treated with an Et_2O solution of oxalic acid to afford the crude salt; recrystallization from absolute EtOH/anhydrous Et_2O gave 0.29 g (67%) of **33** as white crystals: mp 208–210 °C. Anal. ($C_{18}H_{19}BrN_2O\cdot C_2H_2O_4$) C, H, N. See Table 1.

***N,N*-Dimethyl-2-(4-bromo-2,5-dimethoxyphenyl)-1-aminoethane Hydrochloride (9). Method B.** To stirred solution of 2,5-dimethoxyphenethylamine (1.0 g, 5.5 mmol) in glacial HOAc (4 mL) was added a solution of bromine (1.1 g) in HOAc (3 mL). The reaction mixture was stirred overnight at room temperature. The precipitate was collected by filtration and washed with anhydrous Et_2O (3 × 10 mL) to afford 1.4 g of the product (HBr salt) as a white crystalline solid: mp 198–201 °C. A portion of the hydrobromide salt was converted to the free base; a stirred mixture of 2-(4--bromo-2,5-dimethoxyphenyl)-1-aminoethane (0.075 g, 0.28 mmol), 97% formic acid (0.35 g), and 37% formaldehyde (0.5 mL) was heated at 80–95 °C for 24 h. The solution was then concentrated to dryness under reduced pressure. The free base was isolated by the addition of 15% NaOH (0.5 mL) and extraction with Et_2O (3 × 10 mL). The combined organic fractions were dried ($MgSO_4$), and the solvent was removed under reduced pressure. A solution of the free base in anhydrous Et_2O was treated with a saturated solution of HCl gas in Et_2O to give a white solid hydrochloride salt. Recrystallization from 2-PrOH gave 0.06 g (64%) of **9** as white crystals: mp 186–188 °C. Anal. ($C_{12}H_{18}BrNO_2\cdot HCl$) C, H, N.

***N*-Ethyl-2-(4-bromo-2,5-dimethoxyphenyl)-1-aminoethane Hydrochloride (10). Method C.** Acetyl chloride (0.09 g, 1.15 mmol) in dry THF (10 mL) was added dropwise to a stirred solution of 2-(4-bromo-2,5-dimethoxyphenyl)-1-aminoethane (0.3 g, 1.15 mmol) and NEt_3 (0.12 g, 1.15 mmol) in dry THF (10 mL) at 0 °C under a N_2 atmosphere. The solution was allowed to stir at 0 °C over a 1-h period and then stirring was continued at room temperature for 4 h. The mixture was filtered and the solid material was washed with THF (30 mL). The combined filtrate and washings were evaporated under reduced pressure, and the oily residue was dissolved in Et_2O (60 mL), washed successively with 10% HCl (1 mL), 10% $NaHCO_3$ (1 mL), and H_2O (1 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure to afford the desired amide (0.29 g, 84%) as a white solid: mp 95–97 °C. A solution of the amide (0.29 g, 0.96 mmol) in dry THF (3 mL) was slowly added to a cooled (ice bath) solution (1 M) of borane (BH_3) in THF (3 mL) under a N_2 atmosphere. The mixture was heated at reflux for 18 h and cooled on an ice bath, and excess BH_3 was decomposed by careful addition of 6 N HCl (10 mL). The THF was removed by distillation at reduced pressure. The resulting acidic solution was carefully saturated with NaOH pellets. The basic solution was extracted with Et_2O (3 × 30 mL). The combined Et_2O extract was washed with H_2O (10 mL), dried ($MgSO_4$), and evaporated under reduced pressure to give a clear oil. The free base was converted to its hydrochloride salt. Recrystallization of the crude salt from 2-PrOH gave 0.19 g (60%) of **10** as white crystals: mp 224–225 °C. Anal. ($C_{12}H_{18}BrNO_2\cdot HCl$) C, H, N.

***N*-Benzyl-2-(4-bromo-2,5-dimethoxyphenyl)-1-aminoethane Hydrochloride (13). Method D.** A solution of benzoic acid (0.77 g, 6.3 mmol), Et_3N (2.77 mL, 18.9 mmol), and ethyl chloroformate (0.6 mL, 6.3 mmol) in CH_2Cl_2 (40 mL) was allowed to stir at 0 °C for 0.5 h. 2-(4-Bromo-2,5-dimethoxyphenyl)-1-aminoethane (2.0 g, 6.3 mmol) was added and the mixture was allowed to stir for an additional 2 h at room temperature. The mixture was washed with H_2O (20 mL), 0.05 N HCl (10 mL), and H_2O (10 mL), and dried (Na_2SO_4), and the solvent was evaporated under reduced pressure to give 2.1 g (92%) of the desired amide: mp 114–117 °C. The compound was promptly used in the next step without further characterization. A solution of the amide (0.20 g, 0.56 mmol) in dry THF (3 mL) was slowly added to a solution (1 M) of BH_3 in THF (5.8 mL, 5.8 mmol) at 0 °C under a N_2 atmosphere. The mixture was heated at reflux for 18 h, and then cooled in an ice bath, and excess BH_3 was decomposed by careful addition of 6 N HCl (12 mL). The THF was removed by distillation at atmospheric pressure. The resulting acidic solution was carefully saturated with NaOH pellets. The basic solution was extracted with Et_2O (3 × 25 mL). The Et_2O extract was washed with H_2O (10 mL), dried ($MgSO_4$), and evaporated under reduced pressure to give a clear oil. The free base was converted to the hydrochloride salt. Recrystallization of the crude salt from absolute EtOH and anhydrous Et_2O gave 0.11 g (50%) of the *title* compound as colorless needles: mp 202–204 °C. Anal. ($C_{1}37H_{20}BrNO_2\cdot HCl$) C, H, N.

***N*-[2-(4-Bromo-2,5-dimethoxyphenyl)ethyl]piperidine Hydrochloride (14). Method E.** A solution of 2,5-dimethoxyphenylacetic acid (2.0 g, 10.2 mmol) in anhydrous Et_2O (20 mL) was added in a dropwise manner to a slurry of $LiAlH_4$ in anhydrous Et_2O (100 mL) at 0 °C under a N_2 atmosphere. The mixture was allowed to stir at room temperature for 14 h under a N_2 atmosphere. Excess reducing agent was destroyed by careful addition of H_2O (2 mL), 10% NaOH (2 mL), and H_2O (6 mL) at 0 °C. The precipitate was removed by filtration and washed with Et_2O (20 mL). The filtrate was dried ($MgSO_4$) and evaporated under reduced pressure to give 2-(2,5-dimethoxyphenyl)ethanol as a clear oil. Distillation at high vacuum gave 1.5 g (77%) of the product as a clear oil: bp 73–75 °C, 0.08 mmHg (lit.[16] bp 150–153 °C, 8 mmHg); IR (neat) 3386 cm^{-1} (OH), 1500 (C=C, Ar), 1223 (C–O), 1047 (C–O). The compound was used in the next step without further characterization.

p-Toluenesulfonyl chloride (0.24 g, 2 mmol) was added to a solution of 2-(2,5-dimethoxyphenyl)ethanol (0.52 g, 2.6 mmol) in pyridine (1 mL) at 0 °C. The resulting solution was kept in the freezer overnight. Ice-cold H_2O (25 mL) was added and the cloudy mixture was extracted with Et_2O (3 × 25 mL). The combined Et_2O extracts were washed with 0.1 N HCl (25 mL) and H_2O (25 mL). After drying with $MgSO_4$, the solution was evaporated under reduced pressure to yield 0.88 g (97%) of the *p*-toluenesulfonate ester as a thick pale-yellow oil. The compound was promptly used in the next step without further characterization. Piperidine (0.15 mL, 1.5 mmol) was added to a solution of the ester (0.26 g, 0.74 mmol) in CH_3CN at 0 °C. The mixture was headed at reflux for 5 h. After cooling to room temperature, the mixture was diluted with Et_2O (20 mL) followed by H_2O (20 mL). The layers were separated, and the aqueous fraction were extracted with Et_2O (2 × 25 mL). The Et_2O fractions were combined, washed with H_2O (20 mL), and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave 0.16 g (84%) of crude 1-[2-(2,5-dimethoxyphenyl)ethyl]piperidine as a light brown oil: ^1H NMR ($CDCl_3$) δ 6.7 (bs, 3H, ArH), 3.7 (s, 6H, OCH_3), 3.8 (m, 2H, $ArCH_2$), 2.5 (m, 6H, N-CH_2), 1.5 (m, 6H, CH$_2$). A solution of bromine (0.94 mL, 1.8 mmol) in glacial HOAc (3 mL) was slowly added to a solution of the oil (0.15 g, 0.6 mmol) in glacial HOAc (9 mL) at 0 °C. After the addition, the mixture was allowed to stir at room temperature for 5 h. The solvent was evaporated under reduced pressure and the oily residue was dissolved in H$_2$O (25 mL). The aqueous solution was made basic with 10% NaOH and extracted with Et$_2$O (3 × 25 mL), and the combined Et$_2$O extract was dried and evaporated in vacuo to give the free base as an oil. The free base was converted to the HCl salt and recrystallized from absolute EtOH and anhydrous Et$_2$O to give 0.04 g (18%) of the title compound as a white amorphous solid: mp 225–227 °C. Anal. ($C_{15}H_{22}BrNO_2{\cdot}HCl$) C, H, N.

5-Methoxy-3-(2-piperidinoethyl)indole Oxalate (30). Method F. Oxalyl chloride (2 mL, 23.7 mmol) in anhydrous Et$_2$O (25 mL) was added in a dropwise manner to a solution of 5-methoxyindole (2.3 g, 16.7 mmol) in anhydrous Et$_2$O (45 mL). The reaction mixture was allowed to stir at 0 °C for 30 min. The suspension was diluted with petroleum ether (100 mL). The orange solid was collected by filtration and air-dried to provide 3.0 g (75%) of 5-methoxy-3-indoleglyoxyloyl chloride which was used without further purification. The glyoxyloyl chloride (300 mg, 1.26 mmol) in anhydrous Et$_2$O (25 mL) was mixed with a solution of piperidine (536 mg, 6.3 mmol) in anhydrous Et$_2$O and the mixture was allowed to stir at 0 °C for 2 h. The solid was collected by filtration and recrystallized from absolute EtOH to provide 310 mg (86%) of 1-[(5-methoxyindolyl-3)glyoxyloyl]piperidine: mp 180–182 °C. The amide (200 mg, 0.7 mmol) in THF (25 mL) was treated with LiAlH$_4$ (50 mg, 1.32 mmol) under a N$_2$ atmosphere. The mixture was allowed to stir at 0 ° C for 1 h and then at room temperature for 18 h. The hydride was decomposed at ice-bath temperature by the cautious addition of H$_2$O (3 mL), 10% NaOH (3 mL), and H$_2$O (3 mL). The entire mixture was filtered and the filtrate was concentrated under reduced pressure. The product was extracted with Et$_2$O (3 × 20 mL) and the combined ethereal portions were dried (Na$_2$SO$_4$), and evaporated in vacuo. The residue was dissolved in anhydrous Et$_2$O (5 mL) and treated with ethereal solution of oxalic acid. The salt was recrystallized from absolute EtOH to afford 73 mg (30%) of **30**: mp 138–140 °C. Anal. ($C_{15}H_{22}N_2O{\cdot}C_2H_2O_4{\cdot}H_2O$) C, H, N.

3-[2-(*N*-(4-Methylbenzyl)amino)ethyl]-5-methoxyindole Hydrochloride (35). Method G. *p*-Toluoyl chloride (0.16 g, 1.05 mmol) in dry THF (10 mL) was added in a dropwise manner to a stirred solution of 5-methoxytryptamine (0.2 g, 1.05 mmol) and Et$_3$N (0.11 g, 1.05 mmol) in dry THF and allowed to stir at room temperature for 6 h. The mixture was filtered and the solid material was washed with THF (20 mL). The combined filtrate and washings were evaporated under reduced pressure, and the oily residue was dissolved in Et$_2$O (50 mL), washed successively with 10% HCl (1 mL), 10% NaHCO$_3$ (1 mL), and H$_2$O (1 mL), and dried (MgSO$_4$). The solvent was removed under reduced pressure to give a clear oil of the amide intermediate in 70% yield (0.23 g). A solution of the amide (0.23 g, 0.74 mmol) in dry THF (10 mL) was added in dropwise fashion to a stirred suspension of LiAlH$_4$ (0.07 g, 1.83 mmol) in dry THF (10 mL) under a N$_2$ atmosphere. The reaction mixture was heated at reflux for 18 h and cooled at 0 °C on an ice bath, and H$_2$O (0.5 mL) was added. The insoluble salts were removed by filtration and washed with Et$_2$O (3 × 15 mL). The organic portions were combined and dried (MgSO$_4$), and solvent was removed under reduced pressure to afford a crude oil (0.2 g). The free base of the title compound was isolated by flash chromatography using silica gel (eluted, 95:5, CH$_2$Cl$_2$/MeOH). An anhydrous Et$_2$O solution of the free base was treated with HCl gas to afford the crude salt; recrystallization from 2-PrOH gave 0.1 g (42%) of **35** as white crystals: mp 158–159 °C. Anal. ($C_{19}H_{22}N_2O{\cdot}HCl$) C, H, N.

3-[2-(*N*-(4-Aminobenzyl)amino)ethyl)]-5-methoxyindole Oxalate (36). Method H. 10% Pd/C (0.05 g) was added to a solution of 3-[2-(*N*-(4-nitrobenzoyl)amino)ethyl]-5-methoxyindole (intermediate amide in the synthesis of **37**) and (0.25 g, 0.74 mmol) in absolute EtOH (50 mL). The mixture was hydrogenated at 45 psi for 4 h and filtered over a Celite pad, and the solvent was evaporated under reduced pressure to afford the desired amide (0.21 g, 93%) as a while solid: mp 173–174 °C. A solution of AlH$_3$ in anhydrous Et$_2$O was prepared by addition of LiAlH$_4$ (0.14 g, 3.75 mmol) to a stirred solution of AlCl$_3$ (0.15 g, 1.1 mmol) in anhydrous Et$_2$O (20 mL) at 0 °C under a N$_2$ atmosphere. The suspension was stirred 30 min at room temperature, then a solution of the above amide (0.2 g, 0.65 mmol) in a mixture of anhydrous Et$_2$O (10 mL) and dry THF (5 mL) was added in a dropwise manner with stirring. The reaction mixture was allowed to stir for 7 h at room temperature. Excess AlH$_3$ was decomposed by the addition of crushed ice (1 g) and a 10% NaOH solution (5 mL) at 0 °C. The insoluble salts were removed by filtration and washed with Et$_2$O (3 × 20 mL). The combined filtrate and washings were evaporated under reduced pressure, and a solution of the residual oil in Et$_2$O (50 mL) was washed with H$_2$O (2 × 10 mL) and dried (MgSO$_4$). The Et$_2$O solution of the amine was treated with an Et$_2$O solution of oxalic acid to afford the crude salt; recrystallization from MeOH/anhydrous Et$_2$O solution of oxalic acid to afford the crude salt; recrystallization from MeOH/anhydrous Et$_2$O gave 0.09 g (33%) of **36** as white crystals mp: 182–185 °C. Anal. ($C_{18}H_{21}N_3O{\cdot}1.75C_2H_2O_4$) C, H, N.

***N*-(4-Phenylbutyl)-1-(4-bromo-2,5-dimethoxyphenyl)-2-aminopropane Hydrobromide (4). Method a.** Ethyl chloroformate (0.43 g, 4 mmol) was added in a dropwise manner to a stirred solution of 4-phenylbutyric acid (0.66 g, 4 mmol) and Et$_3$N (0.41 g, 4 mmol) in CH$_2$Cl$_2$ (30 mL) at 0 °C, and stirring was continued at 0 °C for 0.5 h. 1-(2,5-Dimethoxyphenyl)-2-aminopropane (0.78 g, 4 mmol) in CH$_2$Cl$_2$ (10 mL) was added in a dropwise fashion and the mixture was allowed to stir for an additional 4 h at room temperature. The reaction mixture was washed with H$_2$O (10 mL), 5% HCl (10 mL), and H$_2$O (2 × 10 mL). The CH$_2$Cl$_2$ portion was dried (MgSO$_4$) and evaporated in vacuo. The white precipitate was washed with Et$_2$O (3 × 15 mL) and recrystallized from 95% EtOH to afford 0.83 g (61%) of the intermediate amide: mp 80 °C. The amide (0.72 g, 2 mmol) in dry THF (30 mL) was added in a dropwise manner to a stirred suspension of LiAlH$_4$ (0.5 g) in dry THF (30 mL) in 0 °C under N$_2$ atmosphere. The reaction mixture was heated at reflux for overnight, and excess LiAlH$_4$ was decomposed at 0 °C with H$_2$O (2 mL), 30% NaOH (0.5 mL), and H$_2$O (0.5 mL). The insoluble salts were removed by filtration and washed with THF (3 × 10 mL). The organic portions were combined, and solvent was removed under reduced pressure. A solution of the oily residue in Et$_2$O (15 mL) was washed with H$_2$O (2 × 10 mL) and dried (MgSO$_4$); solvent was removed under reduced pressure to afford a colorless oily residue of amine. An anhydrous Et$_2$O (10 mL) solution of the amine was saturated with HBr gas to yield a crude salt; recrystallization from absolute EtOH/anhydrous Et$_2$O gave 0.65 g (75%) of the intermediate amine hydrobromide as white crystals: mp 145–146 °C. A solution of 48% HBr (0.2 g) in glacial HOAc (3 mL) was added to the above amine (0.24 g, 0.6 mmol) in glacial HOAc (15 mL) in one portion at 0 °C, then bromine (0.13 g, 0.8 mmol) in glacial HOAc (5 mL) was added in a dropwise manner at the same temperature. The reaction mixture was allowed to stir for 1 h at room temperature, and solvent was removed under reduced pressure to give a solid residue. The residue was stirred for 3 h with anhydrous Et$_2$O (20 mL), and the white solid product was collected by filtration, washed with anhydrous Et$_2$O (5 mL), dried, and recrystallized from absolute EtOH/anhydrous Et$_2$O to afford 0.18 g (63%) of **4**: mp 114–115 °C. Anal. ($C_{21}H_{28}BrNO_2{\cdot}HBr$) C, H, N.

Method b. Ethyl chloroformate (0.22 g, 2 mmol) was added in a dropwise manner to a stirred solution of 4-phenylbutyric acid (0.33 g, 2 mmol) and Et$_3$N (0.25 g, 2.5 mmol) in CH$_2$Cl$_2$ (25 mL) at 0 °C. The reaction mixture was allowed to stir at 0 °C for 0.5 h, and 1-(4-bromo-2,5-dimethoxyphenyl)-2-aminopropane[6] (0.55 g, 2 mmol) in CH$_2$Cl$_2$ (10 mL) was added in dropwise fashion. The reaction mixture was stirred at room temperature for 4 h, washed with H$_2$O (10 mL), 5% HCl (10 mL), and H$_2$O (10 mL), and dried (MgSO$_4$). Solvent was removed under reduced pressure to give a pale yellow solid which was stirred with anhydrous Et$_2$O (10 mL) to afford 0.45 g (54%) of the intermediate amide as a white solid: mp 130 °C. AlH$_3$ was prepared by the careful addition of 100% H$_2$SO$_4$ (0.18 mL) in dry THF (4 mL) to a suspension of LiAlH$_4$ (0.2 g, 5 mmol) in dry THF (10 mL) at 0 °C under a N$_2$ atmosphere; a solution of the above amide (0.34 g, 1 mmol) in THF (25 mL) was added in a dropwise manner. The reaction mixture was allowed to stir for 6 h at room temperature. Excess AlH_3 was decomposed by the addition of crushed ice (10 g) and 15% NaOH (20 mL). The mixture was filtered and the residual mass was washed with CH_2Cl_2 (20 mL). The combined filtrate and washing were evaporated under reduced pressure, and the oily residue in Et_2O (40 mL) was washed with H_2O (2 × 10 mL). The Et_2O portion was dried ($MgSO_4$) and solvent was removed under reduced pressure to give the free amine as a yellow oil. A solution of the amine in anhydrous Et_2O (20 mL) was saturated with HBr gas to afford the crude salt. The salt was stirred with anhydrous Et_2O (30 mL) for 6 h at room temperature and recrystallized from absolute EtOH/anhydrous Et_2O to afford 0.04 g (7%) of 4 as a white solid: mp 113–115 °C.

***N*-Benzyl-1-(4-bromo-2,5-dimethoxyphenyl)-2-aminopropane Hydrochloride (6).** Benzoyl chloride (0.14 mL, 1.2 mmol) in $CHCl_3$ (5 mL) was slowly added to a solution of 1-(4-bromo-2,5-dimethoxyphenyl)-2-aminopropane hydrobromide[6] (0.30 g, 0.85 mmol) and Et_3N (0.3 mL, 2.1 mmol) in $CHCl_3$ (10 mL) at 0 °C. After the addition, the mixture was allowed to warm to room temperature and stirring was continued overnight. The mixture was diluted with $CHCl_3$ (10 mL) and washed successively with H_2O (2 × 20 mL), saturated $NaHCO_3$ solution (20 mL), 10% HCl (20 mL), and H_2O (20 mL) and dried (Na_2SO_4). The solvent was evaporated under reduced pressure to give the crude amide as a white solid. *N*-Benzoyl-1-(4-bromo-2,5-dimethoxyphenyl)-2-aminopropane was obtained as white fluffy needles (0.20 g, 63%) after recrystallization from absolute EtOH: mp 189–191 °C. A solution of 1 M BH_3 in THF (8 mL, 8 mmol) was added via syringe to a suspension of the above amide (0.20 g, 0.54 mmol) in dry THF (10 mL) under a N_2 atmosphere. The mixture was heated at reflux overnight. The reaction mixture was cooled to room temperature and 6 N HCl (20 mL) was carefully added. The THF was removed by distillation at atmospheric pressure. The concentrated solution was allowed to cool to room temperature and was made basic with 15% NaOH solution. The basic solution was extracted with Et_2O (3 × 30 mL). The combined extract was washed with H_2O (20 mL) and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave 0.13 g (65%) of the free base as an oil. The free base was converted to the hydrochloride salt and recrystallized from absolute EtOH and anhydrous Et_2O to afford 0.07 g (34%) of product as a fluffy white solid: mp 197–199 °C. Anal. ($C_{18}H_{22}BrNO_2 \cdot HCl$) C, H, N.

Radioligand Binding. Radioligand binding assays were conducted as previously reported in detail.[13,19,20] 5-HT2A receptors in GF6 cells transfected with the human 5-HT2A gene[20] were labeled with [^{3}H]ketanserin (identified as 5-HT2A(K) in Tables 2 and 3) or [^{125}I]DOI (identified as 5-HT2A(D) in Tables 2 and 3), and 5-HT2C receptors in J1 cells transfected with the rat 5-HT1C gene[20] were labeled with [^{3}H]mesulergine. Radioligands and competing drugs were incubated with homogenates at 37 °C for 30 min, filtered through Schleicher & Schuell glass-fiber filters, and counted in Ecoscint (National Diagnostics) in a Beckman 3801 liquid-scintillation counter. Data are expressed as K_i values and represent the mean and SEM of at least two experiments each performed in triplicate.

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