β-Oxygenated Analogues of the 5-HT$_{2A}$ Serotonin Receptor Agonist 1-(4-Bromo-2,5-dimethoxyphenyl)-2-aminopropane

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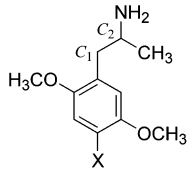
Activation of 5-HT$_{2A}$ serotonin receptors represents a novel approach to lowering intraocular pressure. Because 5-HT$_{2A}$ serotonin receptor agonists might also produce undesirable central effects should sufficient quantities enter the brain, attempts were made to identify 5-HT$_2$ serotonin receptor agonists with reduced propensity to penetrate the blood−brain barrier. 1-(4-Bromo-2,5-dimethoxyphenyl)-2-aminopropan-1-ol (**6**), an analogue of the 5-HT$_2$ serotonin receptor agonist 1-(4-bromo-2,5-dimethoxyphenyl)-2-aminopropane (DOB; **1a**) bearing a benzylic hydroxyl group, was identified as a candidate structure. Of the four optical isomers of **6**, the 1*R*,2*R*-isomer (**6d**; $K_i = 0.5$ nM) was found to bind at 5-HT$_{2A}$ receptors with an affinity similar to that of *R*(−)DOB ($K_i = 0.2$ nM). Like *R*(−)DOB, **6d** behaved as a partial agonist (efficacy ca. 50%) in a 5-HT$_2$-mediated calcium mobilization assay. However, in an in vivo test of central action (i.e., stimulus generalization with rats as subjects), **6d** was >15 times less potent than *R*(−)DOB. O-Methylation of **6d** (i.e., **7d**; 5-HT$_{2A}$ $K_i = 0.3$ nM) resulted in an agent that behaved as a full (93% efficacy) agonist. Intraocular administration of 300 μg of **6d** and **7d** to ocular hypertensive monkeys was shown to reduce intraocular pressure by 20−27%. Given the route of administration (i.e., topical), and concentrations necessary to reduce intraocular pressure, compounds such as **6d** should demonstrate minimal central effects at potentially useful therapeutic doses and offer useful leads for further development.

Compounds that function as efficient agonists at 5-HT$_{2A}$ serotonin receptors have been proposed as novel agents with the potential to control intraocular pressure in the treatment of ocular hypertension and glaucoma.[1] Agents with agonist action at brain 5-HT$_{2A}$ receptors have also been demonstrated to be psychoactive in humans.[2] However, a recent study has found that a local ocular site of action seems to be sufficient for achieving decreased intraocular pressure in a primate model of ocular hypertension.[1] Hence, a 5-HT$_{2A}$ serotonin receptor agonist that does not readily penetrate the blood−brain barrier should be effective following local ocular application, and central side effects should be minimized.

The goal of the present investigation was to develop a novel 5-HT$_{2A}$ serotonin receptor agonist with reduced ability to penetrate the blood−brain barrier. The general approach to achieving this goal was to incorporate a polar moiety into an agent that already possesses 5-HT$_{2A}$ serotonin receptor agonist actions in order to decrease its lipophilicity. Pharmacophore-based design might provide an effective means to accomplish this task. Currently, the two largest categories of 5-HT$_{2A}$ serotonin receptor agonists are the indolealkylamines (e.g. tryptamine analogues) and the phenylalkylamines.[2] Because the former are notoriously nonselective,[2] we focused on the latter, which includes agents such as 1-(4-bromo-2,5-dimethoxyphenyl)-2-aminopropane (DOB, **1a**)



1a X = -Br
1b X = -I
1c X = -Me

and its iodo and methyl counterparts (**1b** and **1c**, respectively). We introduced [^{3}H]DOB and [^{125}I]DOI years ago as radioligands for labeling 5-HT$_2$ receptors, and DOM and *R*(−)DOI are commonly employed as 5-HT$_2$ serotonin receptor agonists in behavioral studies (reviewed in ref 2). DOB (**1a**) is perhaps one of the best studied 5-HT$_{2A}$ serotonin receptor agonists. In various functional assays, DOB (**1a**) has been shown to behave either as a full agonist or partial agonist,[3,4] and this property is associated principally with the *R*-(−)-isomer; *S*(+)DOB is of lower efficacy than its enantiomer.[3] Previous pharmacophoric studies have identified the dimethoxy substitution pattern of DOB as contributing to its actions.[2] In fact, structure−affinity relationships have been examined in detail, and nearly every position of DOB (**1a**) has been investigated. The question at hand was, where in the molecule might a polar substituent

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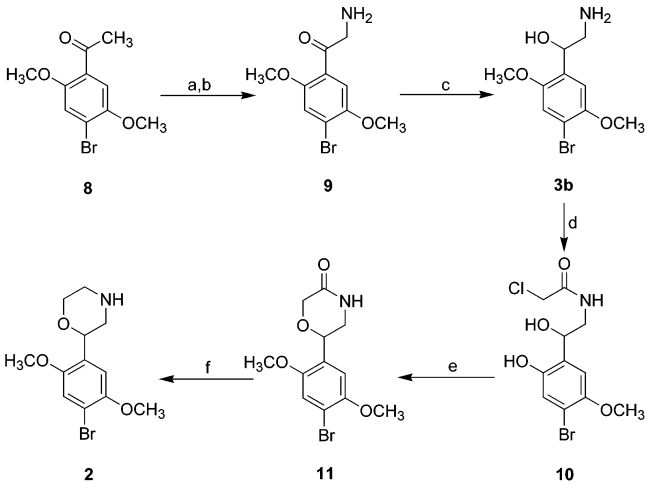
Scheme 1[a]



[a] Reagents and conditions: (a) $Br_2/CHCl_3$, 5 °C to room temperature, 2 h; (b) $(CH_2)_6N_4/CHCl_3$, 50 °C, 1 h, then HCl/EtOH, 50 °C, 3 h; (c) $NaBH_4$/MeOH, 0 °C; (d) $ClCH_2COCl/NaOH/H_2O/CH_2Cl_2$, 0 °C to room temperature, 2 h; (e) KOH/EtOH, 12 h, room temperature; (f) BH_3−THF, reflux, 12 h.

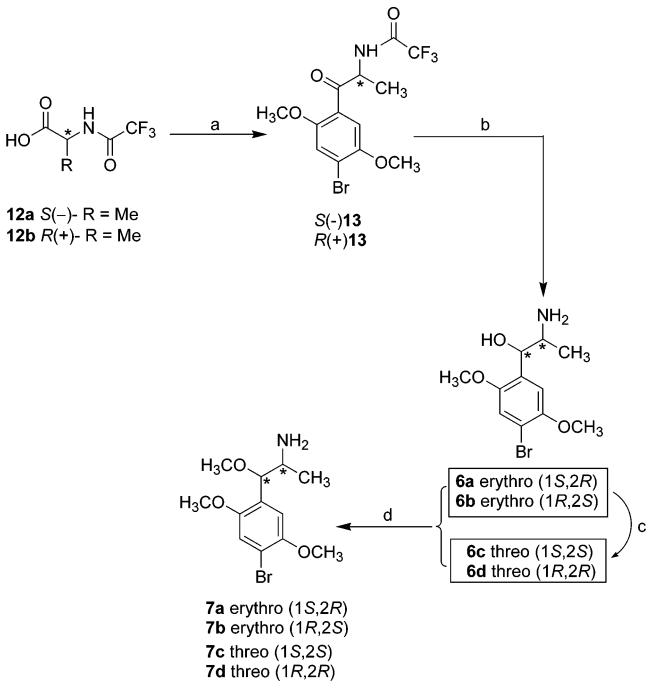
be introduced without significant loss of agonist action? For example, introduction of polar substituents, depending upon the ring-position and the specific substituent, can result in phenylalkylamines that lack affinity for 5-HT_{2A} receptors;[3] in other instances, action has been converted from agonist to low-efficacy partial agonist or even antagonist activity.[5] Quaternization of the terminal amine, a strategy often employed to reduce blood−brain barrier permeability, was not an option here, because the quaternary amine analogue of DOB does not bind at 5-HT_{2A} receptors.[3] The one position of DOB-type compounds that has not been extensively investigated is the benzylic (i.e., C_1 or β-) position. Accordingly, we began this investigation by examining the influence on 5-HT_{2A} affinity and efficacy of polar (i.e., oxygen-bearing) substituents at the benzylic position of DOB-related compounds.

Chemistry

The synthesis of morpholine **2** (Scheme 1) began with **8**; acetylation of commercially available 1-bromo-2,5-dimethoxybenzene under Friedel−Crafts conditions according to a literature procedure,[6] followed by bromination, gave a bromoacetyl intermediate that was transformed through a Sommelet reaction into amino ketone **9** (isolated as its HCl salt). Crude compound **9** was reduced with $NaBH_4$ to provide amino alcohol **3b**. Treatment of **3b** with $ClCH_2COCl$ afforded the corresponding *N*-chloroacetyl derivative **10**, which was converted into morpholinone **11** by base-catalyzed cyclization.[7] Reduction of **11** with BH_3−THF complex gave the desired morpholine **2**. Compound **3b** was prepared as an intermediate in the synthesis of **2**, and compound **3c** was prepared from 2,5-dimethoxy-4-bromobenzaldehyde as described in the literature.[8]

Compounds **12a** and **12b** (Scheme 2), as well as **12c** (where R = *S*-(−)-Et), were prepared from commercially available optically active amino acids by trifluroacetylation according to literature procedures.[9−11] The resulting *N*-trifluroacetyl α-amino acids were then treated with oxalyl chloride to form the appropriate acid chlorides. The acid chlorides were not purified but, following evaporation of solvent, were subjected to a Friedel−Crafts reaction with 1-bromo-2,5-dimethoxybenzene under mild conditions with complete preservation of configurational identity of the products *S*(−)**13** and *R*(+)**13**. The chiral purity of *S*(−)**13** and *R*(+)**13** was established by examination of their proton NMR spectra in the presence of the chiral shift reagent Eu(hfbc).[12] Chiral shift NMR analysis revealed none of the opposite enantiomer, indicating a chiral purity of >98% for each isomer. *Erythro* isomers **6a** and **6b** were prepared by the highly *erythro*-selective reduction[13] of the corresponding ketones *R*(+)**13** and *S*(−) **13**, respectively, with dimethylphenylsilane in TFA. These erythro isomers were also successfully converted into their corresponding threo isomers **6c** and **6d** by utilizing a modification of a procedure that was previously described for the preparation of *threo*-norpseudoephedrine isomers.[14] The structures of all erythro and threo isomers were supported by ^{1}H NMR spectrometry; the erythro isomer **6a** and **6b** showed a signal at δ 5.06 (*CH*-OH), whereas *threo* isomers **6c** and **6d** displayed a signal at δ 4.84 (*CH*-OH). Such a spectroscopic trend is consistent with literature observations.[15] Alkylation of compounds **6a**−**d** with CH_3I afforded methoxy derivatives **7a**−**d**. Although the enantiomeric purity of the trifluoroacetylated intermediate leading to **5b** was not examined, the erythro isomer **5b** was synthesized in a similar manner.

Scheme 2[a]



[a] Reagents and conditions: (a) $(COCl)_2/CH_2Cl_2$, 1-bromo-2,5-dimethoxybenzene/$TiCl_4$, −50 °C to room temperature, 60 h; (b) $SiH(CH_3)_2Ph$/TFA, −5 °C, 2 h then K_2CO_3, reflux, 2 h; (c) Ac_2O, room temperature to 110 °C, 1 h, then 60% H_2SO_4, 110 °C, 1 h; (d) NaH/THF, 0 °C to room temperature 0.5 h, then MeI, reflux, 1 h.

Results and Discussion

Radioligand binding data and the results of a functional assay are provided in Table 1. One of the first compounds prepared and examined in this investigation was morpholine analogue **2**. Compound **2** bears an ether

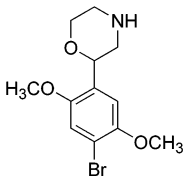
Table 1. Radioligand Binding and Functional Data for Compounds Examined

	stereochemistry		K_i,		EC_{50},		%	
	C_1 (β)	C_2 (α)	nM	SEM	μM[a]	SEM	efficacy	SEM
DOB (**1a**)		(±)	0.10	0.04	0.06	0.03	38	1
		R	0.20	0.04	0.02	0.01	51	2
2	(±)		20.6	1.8			4	1
3b	(±)		2.1	0.5			8	1
3c	(±)		2.0	0.5	0.12	0.02	63	1
4		R	9.2	4.6	0.74	0.03	34	3
5a		(±)	7.6	5.1			15	6
5b	R	S	20.3	2.1			5	2
			Hydroxy Series					
6a	S	R	9.2	3.1			20	6
6b	R	S	1.1	0.1	0.84	0.42	22	5
6c	S	S	10.0	0.1			16	3
6d	R	R	0.5	0.1	0.10	0.01	50	4
			Methoxy Series					
7a	S	R	17.4	0.8	5.04	3.74	49	5
7b	R	S	0.8	0.1	1.33	0.13	54	7
7c	S	S	6.0	0.2	1.41	0.23	31	2
7d	R	R	0.3	0.1	0.13	0.01	93	5

[a] Calcium-mobilization assay. EC_{50} value not determined where efficacy ≤20%.

oxygen atom at the benzylic position that is tethered to the terminal amine. However, its 5-HT_{2A} affinity (K_i = 20.6 nM) is 100-fold lower than that of *R*(−)DOB (K_i = 0.2 nM), and its agonist efficacy in the 5-HT_2-mediated calcium mobilization assay is minimal (Table 1). There are several possible explanations for these unfavorable findings. Apart from the molecule possessing a chiral center, the ether oxygen atom might not be tolerated by the receptor and/or the added ethylene "bridge" might not be readily accommodated by the receptor and its presence detracts from affinity. A more plausible explanation, based on prior structure−affinity investigations, is that the secondary amine of **2** contributes to decreased affinity. That is, we have previously shown that addition of small *N*-alkyl substituents can reduce the 5-HT_{2A} receptor affinity of DOB and DOB-related compounds.[16,17]

Consequently, we turned our attention to simpler phenylethylamine derivatives that lacked an *N*-alkyl substituent (e.g. **3**). Compound **3a**, the α-(or C_2-)-



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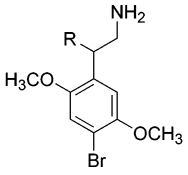
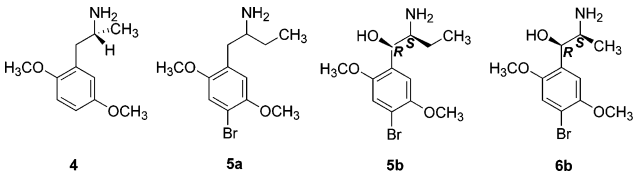


3a R = -H
3b R = -OH
3c R = -OCH_3

desmethyl counterpart of DOB, binds at 5-HT_{2A} serotonin receptors with an affinity comparable to that of DOB (**1a**);[18] that is, the presence of the α-methyl group of DOB is not required for binding. The β-(or C_1-)-hydroxy and -methoxy analogues **3b** and **3c** were prepared for examination as their racemates; compound **3c** had been previously synthesized by Lemaire et al.[8] Hydroxy compound **3b** (K_i = 2.1 nM) displayed 10-fold enhanced affinity relative to **2** but was also a low-efficacy (8%) agonist. In contrast, methoxy compound **3c** (K_i = 2.0 nM) retained the affinity of **3b** and displayed an efficacy (63%) greater than that of racemic DOB (Table 1). These results suggested that not only are polar substituents at the β-position of the phenylalkylamines tolerated by 5-HT_{2A} receptors, certain substituents might even enhance 5-HT_{2A} serotonin receptor agonist efficacy.

Lacking an amine substituent or an α-alkyl group, **3** might be prone to rapid metabolism in vivo by oxidative deamination. Furthermore, although an α-methyl group might not be required for the binding of DOB-type agents at 5-HT_{2A} receptors, we have previously shown that its absence detracts somewhat from 5-HT_{2A} selectivity.[18] Accordingly, we introduced small alkyl groups at the α-position, namely an α-ethyl group and an α-methyl group.

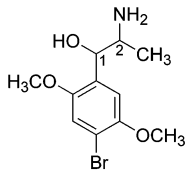
First, however, it was necessary to determine the role of the 4-bromo group on efficacy and whether it should be retained in the analogues to be investigated. Compound **4** (K_i = 9.2 nM), as previously shown,[3] binds with



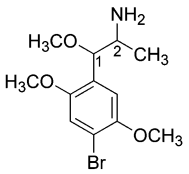
reduced affinity at 5-HT_{2A} receptors relative to *R*(−)DOB. Interestingly, the 4-bromo group does not appear to contribute significantly to efficacy. Compound **4** (EC_{50} = 0.74 μM), although 10-fold less potent than *R*(−)DOB, approximated the efficacy of racemic DOB. That is, the presence of the bromo group contributes both to affinity and agonist potency, but somewhat less to efficacy. Consequently, the bromo function was retained and α-alkyl substituents were introduced. Addition of an α-alkyl substituent introduces a second chiral center, and four optical isomers are possible. For purpose of comparison of the effect of an α-ethyl versus an α-methyl group, we arbitrarily selected as targets the 1*R*,2*S* isomers of a 4-brominated compound. Although there was no a priori reason to suspect that this stereochemistry would be optimal, our immediate goal was simply to compare the influence on affinity/activity of an α-ethyl versus an α-methyl substituent. Standridge et al.[19] have previously synthesized a series of α-ethyl phenylalkylamines including compound **5a**. We found compound **5a** (K_i = 7.6 nM) to bind with high affinity, but with about 70-fold reduced affinity relative to DOB. Furthermore, its 5-HT_{2A} efficacy was only about half that of DOB. Incorporation of the β-hydroxy group reduced affinity (**5b**, 5-HT_{2A} K_i = 20.3 nM) and efficacy (5%) by about 3-fold. In contrast, α-methyl compound **6b** (K_i = 1.1 nM) displayed 20 times the affinity of **5b** while retaining its efficacy.

With information in hand that an α-methyl group is favored over an α-ethyl group, that the 4-bromo substituent should be retained, and that β-hydroxy and β-methoxy substituents are tolerated, the four optical isomers of both β-hydroxy (i.e., **6**) and β-methoxy (i.e., **7**) DOB were prepared for evaluation. As mentioned above, earlier pharmacophoric investigations had already demonstrated that the *R*-isomers of DOB-related agents bind with severalfold higher affinity than their *S*-enantiomers. It was expected, then, that the 2*R*-

isomers would bind with somewhat higher affinity than their 2*S* counterparts. That the 1*S*-hydroxy-2*R*-methyl compound **6**a (K_i = 9.2 nM) binds with nearly 10-fold



6a 1*S*,2*R*
6b 1*R*,2*S*
6c 1*S*,2*S*
6d 1*R*,2*R*



7a 1*S*,2*R*
7b 1*R*,2*S*
7c 1*S*,2*S*
7d 1*R*,2*R*

lower affinity than its 1*R*-hydroxy-2*S*-methyl counterpart **6b** (K_i = 1.1 nM) indicates that 5-HT_{2A} receptors do not readily accommodate the hydroxy group in the *S*-configuration. Similar results were obtained with 1*S*-hydroxy compound **6c** (K_i = 10 nM). Of the four isomers of the hydroxy analogues, the highest affinity member was 1*R*-hydroxy-2*R*-methyl compound **6d** (K_i = 0.5 nM). Parallel results were obtained with the methoxy analogues, and the highest affinity member of the methoxy series was 1*R*-methoxy-2*R*-methyl compound **7d** (K_i = 0.3 nM), and the affinity of **7d** was comparable to that of *R*(−) DOB (K_i = 0.2 nM). It can be concluded that introduction of a β-hydroxy group decreases the affinity of *R*(−)DOB by 50-fold when in the *S*-configuration but has little effect when in the *R*-configuration; likewise, introduction of a β-methoxy group decreases affinity by nearly 100-fold when in the *S*-configuration and is tolerated when in the *R*-configuration.

All the hydroxy and methoxy isomers displayed agonist action. But there is a broad span of potencies. In general, the hydroxy compounds are not as potent as the methoxy isomers; nevertheless, hydroxy compound **6d** (EC_{50} = 0.10 μM), although 5-fold less potent than *R*(−)DOB (EC_{50} = 0.02 μM), was equiefficacious (ca. 50%) in the calcium-mobilization assay. Methoxy compound **7d** possessed similar potency (EC_{50} = 0.13 μM) but was more efficacious than *R*(−)DOB and essentially behaved as a full (93%) agonist.

The intent of this investigation was to identify a 5-HT_{2A} ligand with agonist character and reduced propensity to penetrate the blood−brain barrier. Both **6d** and **7d** bear polar substituents at the benzylic position of a phenylisopropylamine nucleus; although both are similar in 5-HT_{2A} serotonin receptor affinity and agonist potency, **7d** is a full agonist, whereas **6d** displays lower efficacy but an efficacy similar to that of DOB. Because of the presence of the more polar hydroxyl group, **6d** was selected for further evaluation, despite its lower efficacy. Agents with 5-HT_{2A} agonist character have been shown to substitute for DOM (**1c**) in rats trained to discriminate DOM (**1c**) from saline vehicle in a two-lever drug discrimination task (reviewed in ref 20). The effect has been demonstrated to be centrally mediated and is antagonized by 5-HT_{2A} serotonin receptor antagonists.[20] Accordingly, we compared the actions of **6d** with that of the *R*-(−)-isomer of DOB (**1a**). Using rats trained to discriminate 1.0 mg/kg of DOM (**1c**) from saline, administration of *R*(−)DOB resulted in substitution (i.e., stimulus generalization; ED_{50} = 0.09 mg/kg, 95% CL = 0.06−0.16 mg/kg or 0.25 μmol/kg). Administration of **6d** also resulted in substitution (ED_{50} = 1.4 mg/kg; 95% CL = 0.8−2.6 mg/kg, or 4.3 μmol/kg). Evidently, introduction of the benzylic hydroxyl group resulted in a >15-fold rightward shift of the dose−response curve (Figure 1). Another way of viewing the results is that at doses higher than that required for *R*(−)DOB to substitute for the DOM stimulus, **6d** still produced saline-appropriate responding; higher doses of **6d** were required to produce >80% drug-appropriate responding. Given the 5-HT_{2A} affinities and efficacies of these two agents, the results suggest that **6d** might not penetrate the blood−brain barrier as well as *R*(−)DOB.

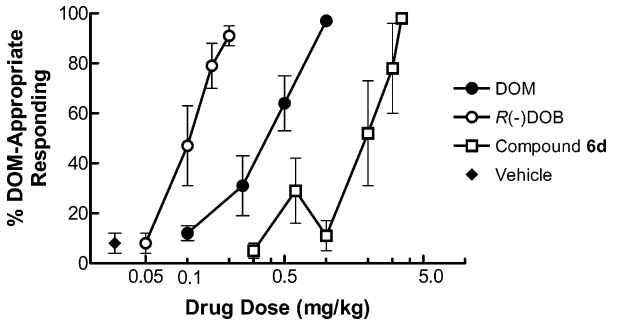


Figure 1. Results [% DOM−appropriate responding ±SEM)] of drug discrimination studies employing rats trained to discriminate DOM (**1c**) (1.0 mg/kg) from saline vehicle. Stimulus generalization was considered to have occurred when the animals made ≥80% of their responses on the DOM-appropriate lever.

Table 2. Intraocular Pressure (IOP, mmHg) Response after Topical Ocular Administration to the Normal Eye of Conscious Cynomolgus Monkeys

compd[a]	baseline IOP	% IOP reduction (SEM) 1 h	3 h	6 h
6d	37.3	10.7(4.1)	19.0[b](3.3)	22.1[b](5.2)
7d	38.0	19.0[b](4.7)	27.5[b](4.3)	25.5[b](5.3)
R(-)DOI[c]	35.5	15.2(4.0)	31.0[b](4.5)	34.4[b](6.7)

[a] 300 μg in phosphate-buffered saline, pH 7.4. [b] p<0.05. [c] Data from May et al.[1] as assayed under comparable conditions.

Encouraged by the drug discrimination results, **6d** and **7d** were assessed for their ability to lower pressure in conscious cynomologus monkeys with laser-induced ocular hypertension. Both compounds effectively decreased intraocular pressure (IOP) following topical ocular application of a 300 μg dose (Table 2). Although further dose−response studies are required to fully characterize the peak IOP reduction, the efficacy of **6d** in the ocular hypertensive monkey coupled with the drug discrimination results suggest that the IOP effect of 5-HT_2 serotonin receptor agonists is mediated by a local rather than centrally mediated mechanism. The maximum reduction in IOP observed for **7d** of 27.5% is similar to that achieved by *R*(−)DOI, an agent routinely used as positive control in such studies.

In conclusion, introduction of a 1*R*-hydroxy (i.e., β-hydroxy) group to *R*(−)DOB is tolerated by 5-HT_{2A} receptors and has relatively little influence on agonist potency or efficacy. In contrast, introduction of a 1*R*-methoxy group, although tolerated by 5-HT_{2A} receptors and having relatively little influence on agonist potency, tends to double efficacy. Additional studies are now planned to further investigate the pharmacology of compounds **6d** (AL-34659) and **7d** (AL-37662). Given the

affinity/potency of these agents and their increased polarity, it is unlikely that they would produce centrally mediated effects at the doses that would be required to reduce intraocular pressure following topical application.

Experimental Section

Chemistry. Melting points were taken in glass capillary tubes on a Thomas-Hoover melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded with a Varian EM-390 spectrometer, and peak position are given in parts per million (δ) downfield from tetramethylsilane as the internal standard. Microanalyses were performed by Atlantic Microlab (GA) for the indicated elements, and the results are within 0.4% of the calculated values. Chromatographic separations were performed on silica gel columns (Kieselgel 40, 0.040−0.063 mm, Merck) by flash chromatography. Reactions and product mixtures were routinely monitored by thin-layer chromatography (TLC) on silica gel precoated F_{254} Merck plates.

Compounds **3a** and **4**, as their HCl salts, were on-hand from previous investigations, and compound **5a**·HCl was a gift from the Research Division of Bristol Laboratories.

(±)2-(4-Bromo-2,5-dimethoxyphenyl)morpholine Oxalate (2). A solution of 1 M BH_3−THF complex (60 mL, 60.0 mmol) was added in a dropwise manner to a solution of **11** (3.16 g, 10.0 mmol) in THF (20 mL) at 0 °C under an N_2 atmosphere. The reaction mixture was heated at reflux for 12 h under an N_2 atmosphere, and concentrated HCl (15 mL) was added in a dropwise manner at −5 °C. The mixture was heated at reflux for an additional 1 h and then the THF was evaporated under reduced pressure. The residue was made alkaline with 1 N NaOH and extracted with CH_2Cl_2 (3 × 50 mL). The combined CH_2Cl_2 portions were washed with H_2O (3 × 50 mL) and dried ($MgSO_4$), and the CH_2Cl_2 was evaporated under reduced pressure to give a colorless oil. The oil in Et_2O/MeOH (4:1) was treated with ethereal oxalic acid; the mixture was concentrated under reduced pressure and the precipitated oxalate salt was collected by filtration, washed with anhydrous Et_2O (3 × 15 mL), and recrystallized twice from 2-PrOH to afford 2.18 g (56%) of **2** as white crystals: mp 190−192 °C; ^{1}H NMR (DMSO-d_6) δ 2.85−3.31 (m, 4H, CH_2), 3.78 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.89−4.19 (m, 2H, CH_2), 4.96 (d, J = 9.0 Hz, 1H, O*CH*), 7.08 (s, 1H, ArH), 7.27 (s, 1H, ArH). Anal. ($C_{12}H_{16}BrNO_3$·$C_2H_2O_4$) C, H, N.

1-Hydroxy-1-(4-bromo-2,5-dimethoxyphenyl)-2-aminoethane Hydrochloride (3b). Bromine (7.99 g, 50 mmol) in $CHCl_3$ (20 mL) was added in a dropwise manner to a stirred solution of 2,5-dimethoxy-4-bromoacetophenone[6] (12.95 g, 50 mmol) in $CHCl_3$ (100 mL) at 5 °C. After the addition was complete, the reaction mixture was allowed to warm to room temperature and stirred for an additional 2 h. The mixture was poured onto crushed ice; the organic portion was separated and washed with H_2O (2 × 100 mL), saturated $NaHCO_3$ solution (2 × 100 mL), and again with H_2O (2 × 100 mL). The solution was dried ($MgSO_4$) and evaporated to dryness under reduced pressure to give a crude brown/white product. The product was recrystallized from MeOH to yield 14.70 g (87%) of the desired bromoacetophenone product as a white solid: mp 122−123 °C; ^{1}H NMR ($CDCl_3$) δ 3.90 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 4.59 (s, 2H, CH_2Br), 7.24 (s, 1H, ArH), 7.41 (s, 1H, ArH).

A solution of the above 2,5-dimethoxy-4-bromo-α-bromoacetophenone (16.90 g, 50 mmol) and hexamethylenetetramine (7.00 g, 50 mmol) in $CHCl_3$ (200 mL) was allowed to stir at 50 °C for 1 h. The reaction mixture was allowed to cool to the room temperature, and the white precipitate was collected by filtration and washed with $CHCl_3$ (3 × 25 mL). The resulting quaternary salt was suspended in a mixture of 95% EtOH (50 mL) and concentrated HCl (25 mL) and heated at 50 °C for 3 h. After 15 min, the reaction mixture was homogeneous and the aminophenone hydrochloride began to crystallize. The mixture was cooled to 0 °C and the white solid was collected by filtration. The solid was recrystallized from H_2O and dried in vacuo over $CaCl_2$ to afford 10.25 g (66%) of crude product as its HCl salt, which was used without further purification. Sodium borohydride (12.48 g, 330 mmol) was added in small portions to a stirred solution of the aminoacetophenone **9** (10.25 g, 33 mmol) in MeOH (250 mL) at 0 °C over 1.5 h. After the addition was complete, the reaction mixture was allowed to stir at 0 °C for an additional 2 h. Solvent was evaporated under reduced pressure, H_2O (150 mL) was added, and the resulting mixture was extracted with CH_2Cl_2 (3 × 75 mL). The combined CH_2Cl_2 portions were washed with H_2O (3 × 50 mL) and dried ($MgSO_4$). Solvent was evaporated under reduced pressure to give the crude free base of **3b** as a yellow-white solid which was purified by recrystallization from MeOH/Et_2O to give the free base of **3b** as white crystals: mp 130−131 °C. The free base in MeOH (50 mL) was treated with ethereal HCl and solvent was evaporated under reduced pressure to give 8.56 g (83%) of **3b** as off-white crystals following recrystallization from 2-PrOH: mp 204−207 °C; ^{1}H NMR (DMSO-d_6) δ 2.69−2.99 (m, 2H, CH_2), 3.77 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 5.02 (m, 1H, *CH*-OH), 6.10 (br.s, 1H, OH, exchangeable), 7.20 (s, 1H, ArH), 7.22 (s, 1H, ArH), 8.02 (br.s, 3H, NH_3^+, exchangeable). Anal. ($C_{10}H_{14}BrNO_3$·HCl·0.5H_2O) C, H, N.

(−)-*erythro*-(1*R*,2*S*)-1-Hydroxy-1-(4-bromo-2,5-dimethoxyphenyl)-2-aminobutane Oxalate (5b). *S*(−)-2-[*N*-(Trifluoroacetyl)amino]-1-(2,5-dimethoxy-4-bromophenyl)-1-butanone was prepared in 29% yield from S(+)-2-trifluoroacetylaminobutyric acid,[11] via trifluoroacetamide **12c**, exactly as described for the synthesis of *S*(−)**13**. The product was isolated as a yellow-white powder: mp 92−94 °C; $[\alpha]_D$ = −5.7° (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.6 Hz, 3H, CH_3), 1.61 (m, 2H, CH_2), 3.93 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 5.58 (m, 1H, CH), 7.28 (s, 1H, ArH), 7.41 (s, 1H, ArH), 7.44 (bs, 1H, NHCO, exchangeable). The butanone was converted to **5b** as described for the synthesis of **6b**, except that ethereal oxalic acid was used in order to isolate the product as the oxalate salt. The salt was recrystallized from MeOH/Et_2O to afford **5b** as white crystals in 76% yield: mp 203−205 °C; $[\alpha]_D$ = −28.5° (*c* 1, MeOH); ^{1}H NMR (DMSO-d_6) δ 0.78 (t, J = 7.3 Hz, 3H, CH_3), 1.33 (m, 2H, CH_2), 3.19 (m, 1H, *CH*-NH_3^+), 3.77 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 5.10 (m, 1H, *CH*-OH), 7.17 (s, 1H, ArH), 7.23 (s, 1H, ArH). Anal. ($C_{12}H_{18}BrNO_3$·$C_2H_2O_4$) C, H, N.

(+)-*erythro*-(1*S*,2*R*)-1-Hydroxy-1-(4-bromo-2,5-dimethoxyphenyl)-2-aminopropane hydrochloride (6a) was prepared from *R*(+)-2-[*N*-(trifluoroacetyl)amino]-1-(2,5-dimethoxy-4-bromophenyl)-1-propanone (*R*(+)**13**), as described for **6b**, as white crystals in 68% yield: mp 194−196 °C; $[\alpha]_D$ = +42.9° (*c* 1, MeOH). Anal. ($C_{11}H_{16}BrNO_3$·HCl·0.5H_2O) C, H, N.

(−)-*erythro*-(1*R*,2*S*)-1-Hydroxy-1-(4-bromo-2,5-dimethoxyphenyl)-2-aminopropane Hydrochloride (6b). Dimethylphenylsilane (1.70 g, 12.5 mmol) was added in a dropwise manner to a solution of (*S*)-(−)-2-[*N*-(trifluoroacetyl)amino]-1-(2,5-dimethoxy-4-bromophenyl)-1-propanone (*S*(−)**13**) (3.84 g, 10.0 mmol) in TFA (5 mL) at −5 °C under an N_2 atmosphere. The reaction mixture was allowed to warm to 0 °C, stirred for an additional 2 h, poured onto crushed ice, and neutralized with a saturated $NaHCO_3$ solution. The solution was extracted with CH_2Cl_2 (3 × 50 mL). The combined CH_2Cl_2 portions were washed with saturated $NaHCO_3$ solution (3 × 25 mL) and brine (3 × 25 mL) and dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. The resulting residue was purified by flash chromatography with silica gel using, sequentially, CH_2Cl_2 and MeOH/CH_2Cl_2 (1:20) as eluants. The crude product in MeOH (30 mL) was added to a stirred mixture of K_2CO_3 (6.91 g, 50 mmol) in H_2O (5 mL) and then heated at reflux for 2 h. The MeOH was removed under reduced pressure and the residue was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic portions were dried ($MgSO_4$), and the solvent was evaporated under reduced pressure to give the crude free base of **6b** as a yellow-white solid. The free base in anhydrous Et_2O (50 mL) was treated with ethereal HCl; the precipitated HCl salt was collected by filtration, washed with anhydrous Et_2O (2 × 10 mL), and recrystallized from EtOAc to afford 2.28 g (70%) of **6b** as white crystals: mp 197−199 °C; $[\alpha]_D$ = −37.1°

(*c* 1, MeOH); ^{1}H NMR (DMSO-d_6) δ 0.92 (d, J = 6.7 Hz, 3H, CH_3), 3.38 (m, 1H, *CH*-NH_3^+), 3.76 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 5.06 (m, 1H, *CH*-OH), 6.06 (d, J = 3.3 Hz, 1H, OH, exchangeable), 7.14 (s, 1H, ArH), 7.23 (s, 1H, ArH), 8.04 (br.s, 3H, NH_3^+, exchangeable). Anal. ($C_{11}H_{16}BrNO_3$·HCl) C, H, N.

(+)-*threo*-(1*S*,2*S*)-1-Hydroxy-1-(4-bromo-2,5-dimethoxyphenyl)-2-aminopropane Hydrochloride (6c). Acetic anhydride (3.57 g, 35.0 mmol) was added to the free base of (−)-*erythro*-(1*R*,2*S*)-1-hydroxy-1-(4-bromo-2,5-dimethoxyphenyl)-2-aminopropane (**6b**) (2.90 g, 10.0 mmol) at room temperature under an N_2 atmosphere. The reaction mixture was heated at 110 °C for 1 h and then cooled to 60−80 °C. Aqueous H_2SO_4 (60%, 8 mL) was added and the reaction mixture was heated at 110 °C for an additional 1 h. The mixture was allowed to cool to room temperature, poured onto crushed ice, and basified with 15% aqueous NaOH solution to pH = 8. The solution was extracted with CH_2Cl_2 (3 × 50 mL). The combined CH_2Cl_2 portions were washed with brine (3 × 50 mL) and dried ($MgSO_4$), and solvent was evaporated under reduced pressure. The resulting residue was purified by flash chromatography [silica gel; CH_2Cl_2/MeOH (4:1)] to give an oil. The oil in anhydrous Et_2O (50 mL) was treated with ethereal HCl. The precipitated HCl salt was collected by filtration, washed with anhydrous Et_2O (2 × 10 mL), and recrystallized from Et_2O/MeOH to afford 2.67 g (82%) of **6c** as white crystals: mp 213-214 °C; $[\alpha]_D$ = +30.9° (*c* 1, MeOH); ^{1}H NMR (DMSO-d_6) δ 1.03 (d, J = 6.7 Hz, 3H, CH_3), 3.27 (m, 1H, *CH*-NH_3^+), 3.76 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 4.84 (m, 1H, *CH*-OH), 6.16 (d, J = 3.3 Hz, 1H, OH, exchangeable), 7.14 (s, 1H, ArH), 7.25 (s, 1H, ArH), 7.98 (br.s, 3H, NH_3^+, exchangeable). Anal. ($C_{11}H_{16}BrNO_3$·HCl) C, H, N.

(−)-*threo*-(1*R*,2*R*)-1-Hydroxy-1-(4-bromo-2,5-dimethoxyphenyl)-2-aminopropane hydrochloride (6d) was prepared, as described for **6c**, from (+)-*erythro*-(1*S*,2*R*)-1-hydroxy-1-(4-bromo-2,5-dimethoxyphenyl)-2-aminopropane (**6a**) as white crystals in 80% yield: mp 214−215 °C; $[\alpha]_D$ = −31.3° (*c* 1, MeOH). Anal. ($C_{11}H_{16}BrNO_3$ × HCl) C, H, N.

(+)-*erythro*-(1*S*,2*R*)-1-Methoxy-1-(4-bromo-2,5-dimethoxyphenyl)-2-aminopropane oxalate (7a) was prepared, as described for **7b**, from (+)-*erythro*-(1*S*,2*R*)-1-hydroxy-1-(4-bromo-2,5-dimethoxyphenyl)-2-aminopropane (**6a**) as a white crystals in 67% yield: mp 189−192 °C; $[\alpha]_D$ = +58.2° (*c* 1, MeOH). Anal. ($C_{11}H_{16}BrNO_3$·$C_2H_2O_4$) C, H, N.

(−)-*erythro*-(1*R*,2*S*)-1-Methoxy-1-(4-bromo-2,5-dimethoxyphenyl)-2-aminopropane Oxalate (7b). A solution of free base of (−)-*erythro*-(1*R*,2*S*)-1-hydroxy-1-(4-bromo-2,5-dimethoxyphenyl)-2-aminopropane (**6b**) (2.90 g, 10.0 mmol) in THF (10 mL) was added in a dropwise manner to a suspension of 95% NaH (0.38 g, 15.0 mmol) in THF (5 mL) at 0 °C under an N_2 atmosphere. After stirring at room temperature for 0.5 h, the reaction mixture was treated in a dropwise manner with CH_3I (1.42 g, 10.0 mmol) at 0 °C and then heated at reflux for 1 h. The mixture was cooled to room temperature and MeOH (3 mL) was added to destroy excess NaH. The solution was concentrated under reduced pressure and diluted with H_2O (10 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 25 mL); the combined CH_2Cl_2 portions were washed with brine (3 × 25 mL) and dried ($MgSO_4$), and solvent was evaporated under reduced pressure to give a crude oil. The oil was purified by flash chromatography (silica gel; CH_2Cl_2/MeOH, 9:1), dissolved in anhydrous Et_2O (50 mL), and treated with an ethereal solution of oxalic acid. The precipitated oxalate salt was collected by filtration, washed with anhydrous Et_2O (2 × 10 mL), and recrystallized from Et_2O/MeOH to afford 2.88 g (73%) of **7b** as white crystals: mp 186−188 °C; $[\alpha]_D$ = −59.8° (*c* 1, MeOH); ^{1}H NMR (DMSO-d_6) δ 0.95 (d, J = 6.8 Hz, 3H, CH_3), 3.27 (s, 3H, CH-OCH_3) 3.40 (m, 1H, *CH*-NH_3^+), 3.78 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.75 (d, J = 2.8 Hz, 1H, *CH*-OCH_3), 6.91 (s, 1H, ArH), 7.30 (s, 1H, ArH). Anal. ($C_{12}H_{18}BrNO_3$·$C_2H_2O_4$) C, H, N.

(+)-*threo*-(1*S*,2*S*)-1-Methoxy-1-(4-bromo-2,5-dimethoxyphenyl)-2-aminopropane oxalate (7c) was prepared, as described for **7b**, from (+)-*threo*-(1*S*,2*S*)-1-hydroxy-1-(4-bromo-2,5-dimethoxyphenyl)-2-aminopropane (**6c**) as white crystals in 52% yield: mp 115−118 °C; $[\alpha]_D$ = +51.7° (*c* 1, MeOH); ^{1}H NMR (DMSO-d_6) δ 0.96 (d, J = 6.7 Hz, 3H, CH_3), 3.14 (s, 3H, CH-OCH_3) 3.40 (m, 1H, *CH*-NH_3^+), 3.78 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.55 (d, J = 8.7 Hz, 1H, *CH*-OCH_3), 6.96 (s, 1H, ArH), 7.32 (s, 1H, ArH). Anal. ($C_{11}H_{16}BrNO_3$·$C_2H_2O_4$) C, H, N.

(−)-*threo*-(1*R*,2*R*)-1-Methoxy-1-(4-bromo-2,5-dimethoxyphenyl)-2-aminopropane oxalate (7d) was prepared, as described for **7b**, from (−)-*threo*-(1*R*,2*R*)-1-hydroxy-1-(4-bromo-2,5-dimethoxyphenyl)-2-aminopropane (**6d**) as white crystals in 73% yield: mp 115−118 °C; $[\alpha]_D$ = −52.2° (*c* 1, MeOH). Anal. ($C_{11}H_{16}BrNO_3$·$C_2H_2O_4$) C, H, N.

(±)-2-(4-Bromo-2,5-dimethoxyphenyl)morpholin-5-one (11). Chloroacetyl chloride (3.39 g, 30 mmol) was added in a dropwise manner to a vigorously stirred mixture of NaOH (0.94 g, 24 mmol) in H_2O (100 mL) and the free base of 1-hydroxy-1-(4-bromo-2,5-dimethoxyphenyl)-2-aminoethane (**3b**) (6.25 g, 20 mmol) in CH_2Cl_2 (100 mL) at 0 °C. After the addition was complete, the reaction mixture was allowed to warm to room temperature and was stirred for an additional 6 h. The layers were separated, and the organic portion was washed with 3% HCl (2 × 25 mL) and saturated $NaHCO_3$ solution (2 × 25 mL) and dried ($MgSO_4$), and solvent was evaporated to dryness under reduced pressure to give 5.00 g (71%) of the crude 1-hydroxy-1-(4-bromo-2,5-dimethoxyphenyl)-2-(chloroacetylamino)ethane (**10**) as a yellow-white foamy semisolid. The product was dissolved in 95% EtOH (50 mL) and added in a dropwise manner to a stirred solution of KOH (1.68 g, 30 mmol) in 95% EtOH (25 mL) at room temperature. The reaction mixture was allowed to stir for an additional 12 h, concentrated under reduced pressure, and diluted with H_2O (80 mL). The mixture was extracted with CH_2Cl_2 (3 × 50 mL); the combined CH_2Cl_2 portions were washed with H_2O (3 × 50 mL) and dried ($MgSO_4$), and CH_2Cl_2 was evaporated under reduced pressure to give 3.58 g (80%) of **11** as white crystals: mp 172−173 °C, after recrystallization from Et_2O/hexanes: ^{1}H NMR ($CDCl_3$) δ 3.24−3.65 (m, 2H, CH_2), 3.80 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.31−4.51 (m, 2H, CH_2), 5.00 (m, 1H, O-*CH*), 6.47 (br s, 1H, *NH*CO, exchangeable), 7.07 (s, 1H, ArH), 7.09 (s, 1H, ArH).

***S*-(−)-2-[*N*-(Trifluoroacetyl)amino]-1-(2,5-dimethoxy-4-bromophenyl)-1-propanone (*S*(−)13).** Oxalyl chloride (11.64 g, 91.8 mmol) was added in one portion to a stirred mixture of *N*-(trifluoroacetyl)-L-alanine[9] (**12a**) (8.00 g, 43.2 mmol) and dry pyridine (0.5 mL) in dry CH_2Cl_2 (300 mL) at 0 °C under an N_2 atmosphere. The reaction mixture was allowed to warm to room temperature and stirred for an additional 2 h. The mixture was concentrated under reduced pressure at a temperature below 30 °C to give an oil. The oil was mixed with 1-bromo-2,5-dimethoxybenzene (9.38 g, 43.2 mmol); the resulting mixture was dissolved in dry CH_2Cl_2 (25 mL) and added in a dropwise manner to a stirred solution of 1 M $TiCl_4$ in CH_2Cl_2 (64.8 mL) at −50 °C under an N_2 atmosphere. The reaction mixture was allowed to warm to room temperature, stirred for an additional 60 h, and poured onto crushed ice. The organic portion was separated and washed successively with 1 M HCl (2 × 50 mL), H_2O (2 × 50 mL), and saturated $NaHCO_3$ solution (2 × 50 mL) and dried ($MgSO_4$), and solvent was removed by evaporation under reduced pressure to give a crude, brown product. The product was purified by flash chromatography (silica gel; CH_2Cl_2) and recrystallized from Et_2O/hexanes to yield 5.97 g (36%) of the title compound as a white solid: mp 144−145 °C; $[\alpha]_D$ = −28.9° (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.43 (d, J = 6.2 Hz, 3H, CH_3), 3.90 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 5.59 (m, 1H, CH), 7.26 (s, 1H, ArH), 7.41 (s, 1H, ArH), 7.61. (br s, 1H, NHCO, exchangeable).

***R*-(+)-2-[*N*-(Trifluoroacetyl)amino]-1-(2,5-dimethoxy-4-bromophenyl)-1-propanone (*R*(+)13).** An exact replication of the above procedure using *N*-(trifluoroacetyl)-D-alanine[10] (**12b**) in place of **12a** gave 6.30 g (38%) of *R*(+)**13** as a white crystals: mp 144−145 °C; $[\alpha]_D$ = +28.4° (*c* 1, MeOH).

Determination of Binding to 5-HT$_{2A}$ Receptor. To determine the relative affinities of serotonergic compounds at the 5-HT$_2$ receptors, their ability to compete for the binding

of the agonist radioligand [^{125}I](±)DOI to brain 5-HT$_{2A}$ receptors was determined as described here with minor modification of a literature procedure.[21] Aliquots of post mortem rat cerebral cortex homogenates (400 μL) dispersed in 50 mM Tris-HCl buffer (pH 7.4) were incubated with [^{125}I](±)DOI (80 pM final) in the absence or presence of methiothepin (10 μM final) to define total and nonspecific binding, respectively, in a total volume of 0.5 mL. The assay mixture was incubated for 1 h at 23 °C in polypropylene tubes, and the assays were terminated by rapid vacuum filtration over Whatman GF/B glass fiber filters previously soaked in 0.3% polyethyleneimine using ice-cold buffer. Nonspecific binding was defined with 1−10 μM methiothepin. Filter-bound radioactivity was determined by liquid scintillation spectrometry on a β-counter. The data were analyzed using a nonlinear, iterative curve-fitting computer program[22] to determine the compound's affinity parameter. The concentration of the compound needed to inhibit the [^{125}I](±)DOI binding by 50% of the maximum (IC_{50} value) was determined for each compound.

Determination of 5-HT$_2$ Activity: [Ca^{2+}]$_i$ Mobilization Assay. The receptor-mediated mobilization of intracellular calcium ([Ca^{2+}]$_i$) was studied using a fluorescence imaging plate reader (FLIPR). Rat vascular smooth muscle cells, A7r5, were grown in a normal media of DMEM/10% FBS and 10 μg/mL gentamycin. Confluent cell monolayers were trypsinized, pelleted, and resuspended in normal media. Cells were seeded in a 50 μL volume at a density of 20 000 cells per well in a black-walled, 96-well tissue culture plate and grown for 2 days. On the day of the experiment, one vial of FLIPR Calcium Assay Kit dye was resuspended in 50 mL of a FLIPR buffer consisting of Hank's balanced salt solution (HBSS), 20 mM HEPES, and 2.5 mM probenecid, pH 7.4. Cells were loaded with the calcium-sensitive dye by addition of an equal volume (50 μL) to each well of the 96-well plate and incubated with dye for 1 h at 23 °C. Typically, test compounds were stored at 25 μM in 50% DMSO/50% ethanol solvent. Compounds were diluted 1:50 in 20% DMSO/20% ethanol. For dose−response experiments, compounds were diluted 1:50 in FLIPR buffer and serially diluted 1:10 to give a five- or eight-point dose−response curve.

At the beginning of an experimental run, a signal test was performed to check the basal fluorescence signal from the dye-loaded cells and the uniformity of the signal across the plate. The basal fluorescence was adjusted between 8000 and 12 000 counts by modifying the exposure time, the camera F-stop, or the laser power. The instrument settings for a typical assay were as follows: laser power, 0.3−0.6 W; camera F-stop, F/2; and exposure time, 0.4 s. An aliquot (25 μL) of the test compound was added to the existing 100 μL dye-loaded cells at a dispensing speed of 50 μL/s. Fluorescence data were collected in real-time at 1.0 s intervals for the first 60 s and at 6.0 s intervals for an additional 120 s. Responses were measured as peak fluorescence intensity minus basal and where appropriate were expressed as a percentage of a maximum 5-HT-induced response.

Acute IOP Response in Conscious Cynomolgus Monkeys. Intraocular pressure was determined with an Alcon pneumatonometer after light corneal anesthesia with 0.1% proparacaine. Eyes were rinsed with saline after each measurement. After a baseline IOP measurement, test compound was instilled in one 30 μL aliquot to the ocular hypertensive eye of eight or nine cynomolgus monkeys. Vehicle was instilled in the test eyes of five or six additional animals. Subsequent IOP measurements were taken at 1, 3, and 6 h. A compound is considered efficacious in hypertensive eyes if there is a decrease from baseline IOP of at least 20% following topical administration.

Drug Discrimination Studies. Seven male Sprague−Dawley rats (Charles River Laboratories), weighing 250−300 g at the beginning of the study, were trained to discriminate (15-min presession injection interval) 1.0 mg/kg of racemic 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane HCl (DOM), obtained as a gift from NIDA, from saline vehicle (sterile 0.9% saline) under a variable-interval 15-s schedule of reward (i.e., sweetened condensed milk) using standard two-lever Coulbourn Instruments operant equipment as previously described.[23] Animal studies were conducted under an approved Institutional Animal Care and Use Committee protocol.

In brief, animals were food-restricted to maintain their body weights at approximately 80% of their free-feeding weight, but were allowed access to water ad lib in their individual home cages. Daily training sessions were conducted with the training dose of the training drugs or saline. For approximately half the animals, the right lever was designated as the drug-appropriate lever, whereas the situation was reversed for the remainder of the animals. Learning was assessed every fifth day during an initial 2.5-min nonreinforced (extinction) session followed by a 12.5-min training session. Data collected during the extinction session included response rate (i.e., responses per minute) and number of responses on the drug-appropriate lever (expressed as a percent of total responses). Animals were not used in the subsequent stimulus generalization studies until they consistently made ≥80% of their responses on the drug-appropriate lever after administration of training drug and ≤20% of their responses on the same drug-appropriate lever after administration of saline for several weeks. During the stimulus generalization (i.e., substitution) phase of the study, maintenance of the training drug/saline discrimination was ensured by continuation of the training sessions on a daily basis (except on a generalization test day). On one of the 2 days before a generalization test, approximately half the animals would receive the training dose of training drug and the remainder would receive saline; after a 2.5-min extinction session, training was continued for 12.5 min. Animals not meeting the original training criteria during the extinction session were excluded from the subsequent generalization test session. During the investigations of stimulus generalization, test sessions were interposed among the training sessions. Once per week, the animals were allowed 2.5 min to respond under nonreinforcement conditions following administration of a dose of DOM (**1c**), *R*(−)DOB·HBr, or **6d**; animals were immediately returned to their individual home cages following the 2.5-min test session An odd number of training sessions (usually five) separated any two generalization test sessions. Doses of test drugs were administered in a random order, using a 15-min presession injection interval, to the group of rats. Stimulus generalization was considered to have occurred when the animals, after a given dose of drug, made ≥80% of their responses (group mean) on the training drug-appropriate lever. Animals making fewer than five total responses during the 2.5-min extinction session were considered as being disrupted. Percent drug-appropriate responding refer only to animals making five or more responses during the extinction session. Where stimulus generalization occurred, an ED_{50} dose was calculated by the method of Finney.[24] The ED_{50} dose represents the drug dose at which animals would be expected to make 50% of their responses on the drug-appropriate lever. All solutions, in sterile 0.9% saline, were freshly prepared daily.

Supporting Information Available: Analysis data for **2**, **3**, **5b**, **6a**−**d**, and **7a**−**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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