refrigerated. The white crystalline precipitate was collected, washed with a minimum of cold H_2O, and dried: yield 422 mg (52%); mp 220 °C dec (lit.[12] mp 189–191 °C dec); UV (H_2O) λ_{max} ($\epsilon \times 10^{-3}$) in pH 1, 277 (8.82); in pH 7, 276 (8.52); in pH 13, 276 (6.39); ^{1}H NMR δ 2.17 (m, $H_{1'}$), 2.76 (d, $H_{5'}$), 3.70 (m, $H_{4'}$), 4.19 (m, $H_{3'}$), 6.09 (t, $H_{1'}$), 8.45 (s, H_6); MS (EI), *m/e* 306 $(M + 1)^+$. Anal. ($C_9H_{12}BrN_3O_4$) C, H, N.

5-Bromo-5′-(bromoacetamido)-2′,5′-dideoxyuridine (8). The title compound, mp 190 °C dec, was prepared in 85% yield from **7** (300 mg, 0.980 mmol) by the procedure described for the preparation of **3**. The analytical sample required drying at 100 °C; UV (EtOH) λ_{max} ($\epsilon \times 10^{-3}$) in pH 1, 279 (8.62); in pH 7, 278 (8.43); in pH 13, 276 (5.77); ^{1}H NMR δ 2.17 (m, 2, $H_{2'}$), 3.38 (m, 2, $H_{5'}$), 3.77 (m, 1, $H_{4'}$), 3.88 (s, 2, CH_2Br), 4.14 (m, 1, $H_{3'}$), 5.30 (s, 1, $O_{3'}H$), 6.08 (t, 1, $H_{1'}$), 8.04 (s, 1, H_6), 8.45 (m, 1, N_5H), 11.83 (s, 1, H_3). Anal. ($C_{11}H_{13}Br_2N_3O_5$) C, H, N.

5′-(Bromoacetamido)-2′,5′-dideoxy-5-iodouridine (10). The title compound, mp 217 °C dec, was prepared in 93% yield from 5′-amino-2′,5′-dideoxy-5-iodouridine (**9**)[12] (155 mg, 0.424 mmol) by a modification of the procedure described for the preparation of **3**. A greater volume of DMAC (20 mL) and longer reaction time (80 min) were required for this reaction. The reaction mixture was filtered before evaporation; UV (EtOH) λ_{max} ($\epsilon \times 10^{-3}$) in pH 1, 287 (6.75); in pH 7, 287 (6.39); in pH 13, 278 (4.61); ^{1}H NMR δ 2.15 (m, 2, $H_{2'}$), 3.35 (m, $H_{5'}$), 3.75 (m, 1, $H_{4'}$), 3.89 (s, 2, CH_2Br), 4.13 (s, 1, $H_{3'}$), 5.30 (d, 1, $O_{3'}H$), 6.03 (t, 1, $H_{1'}$), 8.01 (s, 1, H_6), 8.44 (m, 1, N_5H), 11.68 (s, 1, H_3). Anal. ($C_{11}H_{13}BrIN_3O_5$) C, H, N.

5′-(Bromoacetamido)-2′,5′-dideoxy-5-fluorouridine (12). A solution of **11**[13] (270 mg, 1.10 mmol) in DMAC (5 mL) was treated with 4-nitrophenyl bromoacetate (300 mg, 1.16 mmol) and stirred at 25 °C for 40 min. The solution, containing unreacted **11** and bromoacetate (~40% by TLC), was treated with *N,N*-diisopropylethylamine (87.1 μL, 0.50 mmol), stirred for 30 min, and evaporated to dryness under high vacuum. The residue was triturated and stirred with Et_2O (2 × 10 mL) followed by $CHCl_3$ (2 × 20 mL) to give a homogeneous powder, which was collected, washed with $CHCl_3$, and dried: yield 252 mg (63%); melting point indefinite; UV (MeOH) λ_{max} ($\epsilon \times 10^{-3}$) in pH 1, 267 (8.75); in pH 7, 266 (10.20); in pH 13, 268 (6.81); ^{1}H NMR δ 2.14 (m, 2, $H_{2'}$), 3.36 (m, $H_{5'}$), 3.76 (m, 1, $H_{4'}$), 3.87 (s, 2, CH_2Br), 4.12 (m, 1, $H_{3'}$), 5.33 (m, 1, $O_{3'}H$), 6.10 (t, 1, $H_{1'}$), 7.98 (d, 1, J_{H_6,F_5} = 6.8 Hz, H_6), 8.47 (m, 1, N_5H). Anal. ($C_{11}H_{13}BrFN_3O_5$) C, H, N.

5′-(Bromoacetamido)-2′,5′-dideoxy-5-ethyluridine (14). A solution of **13**[15] (300 mg, 1.18 mmol) in DMAC (15 mL) was cooled in an ice bath, treated with 4-nitrophenyl bromoacetate (321 mg, 1.24 mmol), and stirred at 25 °C for 35 min. The resulting solution was evaporated to dryness at 25 °C under high vacuum and the residue triturated with Et_2O (3 × 30 mL), collected, washed with Et_2O, and dried: yield 416 mg (94%); mp 237 °C dec; UV (MeOH) λ_{max} ($\epsilon \times 10^{-3}$) in pH 1, 266 (9.80); in pH 7, 267 (9.46); in pH 13, 266 (7.18); ^{1}H NMR δ 1.05 (t, 3, CH_3), 2.12 (m, 2, $H_{2'}$), 2.26 (q, 2, CH_2CH_3), 3.34 (m, 2, $H_{5'}$), 3.76 (m, 1, $H_{4'}$), 3.38 (s, 2, CH_2Br), 4.15 (m, 1, $H_{3'}$), 5.32 (d, 1, $O_{3'}H$), 6.15 (t, 1, $H_{1'}$), 7.38 (s, 1, H_6), 8.45 (t, 1, N_5H), 11.28 (s, 1, H_3). Anal. ($C_{13}H_{18}BrN_3O_5$).

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N-Methyl Derivatives of the 5-HT_2 Agonist 1-(4-Bromo-2,5-dimethoxyphenyl)-2-aminopropane

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1-(4-Bromo-2,5-dimethoxyphenyl)-2-aminopropane (DOB) is a serotonin (5-HT) agonist that displays a high affinity and selectivity for a certain population of central 5-HT binding sites (i.e., 5-HT_2 sites). In the present study, (a) an enantiomeric potency comparison was made for the optical isomers of DOB and (b) the activity of *N*-monomethyl-, *N,N*-dimethyl-, and *N,N,N*-trimethyl-DOB was examined. (*R*)-(−)-DOB (K_i = 0.39 nM) was found to have 6 times greater affinity than its *S*-(+) enantiomer at [^{3}H]DOB-labeled (rat cortical homogenates) 5-HT_2 sites; N-methylation of racemic DOB resulted in a decrease in affinity that was at least 1 order of magnitude per methyl group. Similar results were obtained in an in vivo drug discrimination paradigm with rats as subjects and (*R*)-(−)-DOB (0.2 mg/kg) as the training drug. Thus, the *R*-(−) isomer of DOB is more active than its *S*-(+) enantiomer and than any of the possible *N*-methyl derivatives of DOB, both with respect to affinity at central 5-HT_2 binding sites and with respect to potency in the behavioral (i.e., stimulus generalization) studies.

We have recently demonstrated that certain 4-substituted derivatives of 1-(2,5-dimethoxyphenyl)-2-aminopropane are serotonin (5-HT) agonists with a high affinity and selectivity for a particular population of central 5-HT binding sites (i.e., 5-HT_2 sites).[1-4] Amongst the most potent and selective of these agents is 1-(4-bromo-2,5-dimethoxyphenyl)-2-aminopropane (DOB; **1**),[5] which may now be considered a prototypic 5-HT_2 agonist. More recently, we have introduced [^{3}H]DOB as a radioligand for selectively labeling these sites.[6] To date, an enantiomeric

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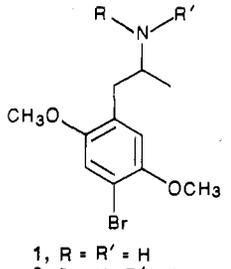
Table I. Affinity of DOB Analogues for 5-HT_2 Binding Sites

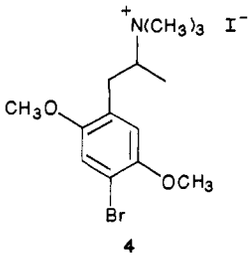
agent	[^{3}H]ketanserin sites[a]		[^{3}H]DOB sites[a]	
	K_i, nM	Hill slope	K_i, nM	Hill slope
(±)-DOB (1)	41 (5)	0.85 (0.04)	0.79 (0.01)	0.90 (0.02)
(*R*)-(−)-DOB	24 (3)	0.80 (0.03)	0.39 (0.01)	0.90 (0.11)
(*S*)-(+)-DOB	145 (9)	0.87 (0.02)	2.3 (0.20)	0.97 (0.02)
N-Me-DOB (2)	79 (6)	0.75 (0.02)	7.7 (1)	0.81 (0.08)
N-Me_2-DOB (3)	380 (20)	0.98 (0.02)	94 (7)	0.87 (0.03)
4 (QDOB)	>25000	*b*	8250 (200)	0.98 (0.09)

[a] Affinities for [^{3}H]ketanserin-labeled and [^{3}H]DOB-labeled 5-HT_2 sites in rat cortical homogenates. K_i values and Hill slopes are followed by ±SEM in parentheses. [b] Value not determined in the present study.

potency comparison has not been made for the affinity of the optical isomers of DOB for [^{3}H]DOB-labeled 5-HT_2 sites. Furthermore, a review of the recent literature reveals that those 5-HT agonists that display a high affinity and/or selectivity for 5-HT_1 binding sites (i.e., 5-HT_{1A} and 5-HT_{1B} sites) usually possess a terminal amine group that is a secondary or tertiary amine.[7] In the course of our work on the structure–activity relationship of DOB,[5] and for purposes of subsequent drug design, it became necessary to determine the relative importance of a primary amine (as is found in DOB) vs. a secondary or tertiary amine. An example of a DOB analogue possessing a quaternized amine was also of interest in that such an agent, by virtue of its anticipated inability to penetrate the blood–brain barrier, might constitute a peripheral 5-HT_2 agonist with minimal central activity. As a consequence, we prepared the *N*-monomethyl, *N*,*N*-dimethyl, and *N*,*N*,*N*-trimethyl derivatives of DOB (**2**–**4**, respectively) and evaluated these agents both in vitro and in vivo (i.e., with respect to their affinities for central 5-HT_2 sites and their discriminative stimulus effects in rats trained to discriminate (*R*)-(−)-DOB from saline).



1, R = R′ = H
2, R = H, R′ = CH_3
3, R = R′ = CH_3



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Results

Each of the agents displayed a higher affinity for [^{3}H]DOB-labeled 5-HT_2 sites than for [^{3}H]ketanserin-labeled 5-HT_2 sites (Table I). Racemic DOB (1) possesses a very high affinity for 5-HT_2 binding sites, with the *R*-(−) isomer displaying 6 times the affinity of its *S*-(+) enantiomer (Table I). The *N*-monomethyl derivative **2** and the dimethyl derivative **3** possess lower affinities, by 1 and 2 orders of magnitude, respectively, than that of racemic DOB at [^{3}H]DOB-labeled 5-HT_2 sites. The quaternary amine analogue of DOB (i.e., QDOB; **4**) is essentially inactive at 5-HT_2 sites regardless of which radioligand is used as the label.

Table II. Results of Stimulus-Generalization Studies with Rats Traned To Discriminate (*R*)-(−)-DOB from Saline

agent	dose[a]	*N*[b]	responding[c]	response rate[d]
(*R*)-(−)-DOB	0.01	4/4	5% (3)	12.5 (2.1)
	0.03	5/5	21% (6)	11.8 (3.4)
	0.05	5/5	58% (12)	12.0 (3.8)
	0.10	4/4	64% (9)	10.8 (2.7)
	0.20	4/4	98% (1)	12.3 (2.4)
	ED50 = 0.05 (0.03–0.09) mg/kg			
(*S*)-(+)-DOB	0.2	3/3	3% (3)	12.0 (0.2)
	0.4	3/4	48% (8)	10.5 (2.8)
	0.7	3/3	63% (9)	10.8 (2.1)
	1.1	4/4	82% (11)	10.8 (3.5)
	ED50 = 0.56 (0.29–1.08) mg/kg			
N-Me-DOB (2)	0.3	3/3	12% (2)	11.6 (1.4)
	0.6	4/4	28% (10)	13.6 (2.4)
	1.0	3/3	50% (12)	12.0 (2.4)
	1.2	3/4	70% (4)	13.3 (4.8)
	1.3	5/5	82% (10)	8.0 (3.5)
	1.4	2/6	*e*	
	1.5	2/6	*e*	
	ED50 = 0.82 (0.47–1.41) mg/kg			
N-Me_2-DOB (3)	2.0	3/4	23% (12)	14.6 (3.0)
	2.2	5/6	6% (5)	14.8 (2.7)
	4.0	4/6	29% (20)	10.1 (3.2)
	6.0	3/5	38% (27)	8.1 (2.6)
	7.5	3/5	64% (15)	6.8 (3.6)
	7.8	3/5[f]	86% (8)	4.5 (1.3)
	8.5	1/4	*e*	
	ED50 = 5.36 (2.96–6.65) mg/kg			
4 (QDOB)	0.7	4/4	3% (1)	16.2 (1.8)
	1.2	3/3	9% (8)	11.9 (2.0)
	2.0	4/4	38% (21)	7.3 (2.7)
	2.2[g]	3/4	3% (3)	3.7 (0.8)
(*R*)-(−)-DOB	0.2	6/6	92% (4)	12.1 (1.9)
saline (0.9%)[h]		6/6	11% (4)	11.8 (2.2)

[a] Dose (milligrams/kilogram). [b] *N* = number of animals responding/number of animals to receive drug. [c] Number of responses made on the (*R*)-(−)-DOB-appropriate lever (as a percent of total responses made during the 2.5-min extinction session). Percent followed by ±SEM. [d] Mean responses per min (during the 2.5-min extinction session), followed by ±SEM. [e] Disruption of behavior (i.e., no responding). [f] One additional animal, disrupted at a lower dose, made only 8% of its responses on the DOB-appropriate lever. [g] Higher doses could not be tested due to solubility problems. [h] Dose = 1 mL/kg.

A group of six rats were trained to discriminate 0.2 mg/kg of (*R*)-(−)-DOB from saline under a variable-interval 15-s schedule of reinforcement.[8] Responding was dose dependent in that lower doses of the training drug resulted in a decrease in (*R*)-(−)-DOB-appropriate responding (ED50 = 0.05 mg/kg) (Table II). In tests of stimulus generalization, the (*R*)-(−)-DOB stimulus generalized to (*S*)-(+)-DOB (ED50 = 0.56 mg/kg), to the *N*-monomethyl derivative **2** (ED50 = 0.82 mg/kg), and to the *N*,*N*-dimethyl derivative **3** (ED50 = 5.36 mg/kg), but did not generalize to the quaternary amine **4** (Table II). It might be noted that doses of greater than 2.2 mg/kg of **4** could not be evaluated due to solubility problems; nevertheless, **4** did not result in stimulus generalization at doses of up to nearly 50 times the ED50 dose of (*R*)-(−)-DOB.

Discussion

[^{3}H]Ketanserin, a 5-HT_2 antagonist, is commonly employed to label central 5-HT_2 binding sites. [^{3}H]DOB is a new radioligand that appears to label the high-affinity

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state of 5-HT_2 binding sites (i.e., 5-HT_{2H} sites).[6,9,10] Serotonin antagonists generally display a similar affinity for 5-HT_2 sites regardless of which radioligand is used to label the sites, whereas serotonin agonists display an affinity for [^{3}H]DOB-labeled sites that is usually 10–100 times greater than their affinity for [^{3}H]ketanserin-labeled sites.[6] The results in Table I are consistent with this generality; nevertheless, the affinities of the *N*-monomethyl, *N,N*-dimethyl, and quaternary amine derivatives of DOB are significantly less than that of DOB at 5-HT_2 sites. These results suggest that the primary amine is important for high affinity.

The results of the drug-discrimination study parallel those of the binding study. (*R*)-(−)-DOB (ED50 = 0.05 mg/kg) is about 10 times more potent than (*S*)-(+)-DOB (ED50 = 0.56 mg/kg), and is 1 and 2 orders of magnitude more potent than the *N*-monomethyl derivative **2** (ED50 = 0.82 mg/kg) and the *N,N*-dimethyl derivative **3** (ED50 = 5.36 mg/kg), respectively. The DOB stimulus did not generalize to **4**, but this is probably a result of its low affinity for 5-HT_2 sites rather than to any problems that might be associated with penetration of the blood–brain barrier.

Whereas tertiary amines lead to enhanced affinity/selectivity of agonists for 5-HT_{1A} sites [e.g., 8-hydroxy-2-(di-*n*-propylamino)tetralin],[7] and secondary amines seem to contribute to affinity/selectivity for 5-HT_{1B} sites [e.g., 1-[3-(trifluoromethyl)phenyl]piperazine; RU 24969],[7] the primary amine derivative DOB (**1**), which displays a low affinity for 5-HT_1 sites,[6] has a higher affinity at ([^{3}H]-DOB-labeled) 5-HT_2 sites, by at least 1 order of magnitude, than its corresponding secondary, tertiary, and quaternary amine analogues.

Experimental Section

Synthesis. Proton magnetic resonance spectra were obtained with a JEOL FX90Q spectrometer with tetramethylsilane as an internal standard; infrared spectra were determined with a Perkin-Elmer 257 spectrophotometer. Spectral data are consistent with assigned structures. Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlab (Atlanta, GA) and determined values are within 0.4% of theoretical. Racemic 1-(4-bromo-2,5-dimethoxyphenyl)-2-aminopropane hydrochloride (**1**) and its *N*-monomethyl derivative (as the HCl salt) **2** were available from previous studies in our laboratory; the HCl salts of (*R*)-(−)-**1** and (*S*)-(+)-**1** were obtained as gifts from NIDA.

***N*-Dimethyl-1-(4-bromo-2,5-dimethoxyphenyl)-2-aminopropane Hydrogen Oxalate (3).** Formic acid (97%, 35 g) was slowly added to 1-(4-bromo-2,5-dimethoxyphenyl)-2-aminopropane (**1**, free base)[5] (7.38 g, 26.9 mmol) while cooling in an ice bath. Formaldehyde (37%, 50 mL) was then slowly added to this cooled solution. The solution was heated at 80-90 °C for 24 h. Vigorous bubbling was observed during the first 2-h period; the solution was allowed to cool to room temperature and was concentrated to dryness under reduced pressure, leaving an off-white solid. This residue was treated with 15% NaOH and extracted with Et_2O. The extract was dried ($MgSO_4$) and the solvent was removed under reduced pressure. Kugelrohr distillation of the residue [68–75 °C (0.03 mmHg)] afforded 6.55 g (81%) of the product (free base) as a viscous oil. A portion of this oil was converted to the oxalate salt by the addition of an ethereal solution of the amine to an excess of oxalic acid in anhydrous Et_2O; the salt was recrystallized from EtOH/Et_2O: mp 160–162 °C. Anal. ($C_{13}H_{20}BrNO_2 \cdot C_2H_2O_4$) C, H, N.

***N,N,N*-Trimethyl-1-(4-bromo-2,5-dimethoxyphenyl)-2-aminopropane Iodide (4).** An excess of iodomethane (2 mL) was added to a stirred solution of **3** (1.20 g, 4.0 mmol) in benzene (20 mL). After the mixture was stirred for 18 h, 1.7 g (96%) of product was collected. An analytical sample was prepared by recrystallization from methanol: mp 215–217 °C dec. Anal. ($C_{14}H_{23}BrINO_2$) C, H, N.

Binding Studies. The radioligand binding assay was conducted in essentially the same manner as reported earlier.[2,5] Frontal cortex homogenates were prepared from male Taconic Farms Sprague–Dawley rats (ca. 200 g) and were either frozen (−30 °C) for later use or used immediately. No differences in binding were noted between the two preparations. Membrane homogenates were prepared in 50 mM Tris·HCl (pH 7.4 at 37 °C) buffer containing 10 mM $MgSO_4$, 0.5 mM Na_2EDTA, 0.1% ascorbic acid, and 10 μM pargyline. The assays were performed in triplicate in 2.0 mL of buffer to which membranes (3 mg wet weight for [^{3}H]ketanserin binding, and 20 mg wet weight for [^{3}H]DOB binding]) were added last. Competition experiments at 11 concentrations of nonradioactive drug were performed with tritiated ligands obtained from New England Nuclear; 0.4 nM [^{3}H]ketanserin (90.4 Ci/mmol) or [^{3}H]DOB (40 Ci/mmol) were used to label 5-HT_2 sites. Nonspecific binding was measured with 1 μM cinanserin. Filtration was accomplished with glass fiber filters (Schleicher and Schuell) followed by a 10-mL wash with the experimental buffer. Filters were counted by liquid scintillation spectrometry with NEN 963 in a Beckman 3801 scintillation counter at an efficiency of 50%. Competition data were analyzed by a computer-assisted nonlinear least-squares regression analysis to obtain IC_{50} values and pseudo Hill coefficients. K_i values were calculated according to the equation $K_i = IC_{50}/(1 + [D]/K_D)$, where [D] = concentration of radioligand and K_D is the equilibrium dissociation constant of radioligand binding.

Discrimination Studies. In the present study, male Sprague–Dawley rats ($n = 6$) were trained to press both levers of a standard two-lever operant chamber (Coulbourn Instruments Model E10-10) for food (sweetened milk) reward. Once the animals responding was consistent, they were trained to discriminate intraperitoneal injections of 0.2 mg/kg of (*R*)-(−)-DOB·HCl from 1.0 mL/kg of 0.9% sterile saline (administered 15 min prior to testing) with a variable-interval (15 s) schedule of reinforcement, such that after administration of the training dose of the training drug the animals eventually made >80% of their responses on the (*R*)-(−)-DOB-appropriate lever, whereas, after administration of saline, the animals made <20% of their responses on this same lever. Training sessions were of 15-min duration. The training procedure and criteria are virtually identical with those that we recently reported using 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane as the training drug;[2] a detailed description of the following testing procedure is also given therein. In tests of stimulus generalization (during which maintenance of the original DOB/saline discrimination was insured by continuation of training sessions throughout the studies), the animals were allowed 2.5 min to respond under extinction conditions and were then returned to their individual home cages. An odd number of training sessions (usually five, but never less than three) separated any two test sessions. During the test sessions, doses of the challenge drugs were administered by ip injection in a random order to, routinely, groups of three to six animals. A 15-min presession injection interval was used throughout. Stimulus generalization was said to have occurred when the animals made greater than 80% of their responses on the DOB-appropriate lever. Animals making less than five total responses during the entire 2.5-min extinction session were reported as being disrupted. Where stimulus generalization occurred, ED50 values (i.e., doses at which the animals would be expected to make approximately 50% of their responses on the drug-appropriate lever) were calculated from the dose–response data.

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