Behavioral and Serotonin Receptor Properties of 4-Substituted Derivatives of the Hallucinogen 1-(2,5-Dimethoxyphenyl)-2-aminopropane

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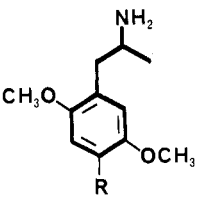
The serotonin (5-HT) receptor affinities and behavioral (discriminative stimulus) properties of a series of 4-substituted derivatives of 1-(2,5-dimethoxyphenyl)-2-aminopropanes (2,5-DMA) were investigated. The substituents at the 4-position included H, OMe, OEt, Me, Et, F, Br, I, and NO_2. Substituent lipophilicities (π values) of these functionalities appear to have a minimal effect on either 5-HT receptor affinity or behavioral activity. Those derivatives previously found to be most potent in human studies possess significant affinity for 5-HT receptors. Furthermore, when rats trained to discriminate (±)-1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM) from saline were used, generalization was found to occur upon administration of the 4-substituted 2,5-DMA derivatives. Because a direct relationship exists between the ED_{50} values obtained from these discrimination studies and human hallucinogenic potencies, the discriminative stimulus paradigm, with DOM as a training drug, appears to be a useful tool for comparing the quantitative and qualitative (DOM-like) effects produced by certain hallucinogenic agents.

In man, 1-(2,5-dimethoxyphenyl)-2-aminopropane (2,5-DMA, 1) is hallucinogenic.[1] Substitution at the 4-position



	R
1	H
2	OCH_3
3	OC_2H_5
4	CH_3
5	C_2H_5

of 2,5-DMA by a methoxy (2,4,5-TMA, 2), ethoxy (3), methyl (DOM, 4), or ethyl (DOET, 5) group increases the potency of the parent compound by two- to tenfold.[1] 4-Bromo (DOB, 7) and 4-iodo (DOI, 8) substitution result in an even further enhancement in activity, although there is some question as to whether these compounds produce behavioral effects similar to those of 1–4.[1] Examination of a series of 4-alkyl-substituted 2,5-DMA analogues, including the 4-*n*-propyl (DOPR), 4-*n*-butyl (DOBU), 4-*tert*-butyl (DOTB), and 4-amyl (DOAM) derivatives, in both human and animal studies, again reveals a dependence of activity on the nature of 4-position substituent.[1-4]

How does this 4-substituent alter the potency of these agents? The presence of a substituent at this position apparently hinders the metabolism of 2,5-DMA;[1] however, this explanation does not adequately account for the observed range of activities within this series. That is, although metabolic studies have not been performed for all possible 4-substituted phenylisopropylamines, if the presence of such a substituent served merely to retard metabolism, a large range of activities might not be anticipated for these agents. It has been reported that the log *P* (octanol–water partition coefficient) of substituted phenylisopropylamines might be a significant determinant of hallucinogenic potency, in as much as it might be related to their distributional characteristics.[5] However, recent studies reveal that activity cannot be accounted for by log *P* alone and that log *P* consistently overestimates the potencies of agents with certain substitution patterns, while it underestimates the potencies of others.[6] There is evidence that the substituent at the 4-position of various phenylisopropylamines might directly interact with receptors;[7,8] to this extent, there appears to be a correspondence between serotonin (5-HT) receptor activation,[7] as well as with human hallucinogenic potency,[2] and the lipophilic character of the 4-position substituent (as reflected by, for example, π values or substituent lipophilicities). An examination of a series of 13 phenylisopropylamine derivatives revealed a correlation ($r^2 = 0.81$) between their hallucinogenic potencies and the π values of their 4-position substituents (i.e., π_4).[6] Although π_4 appears to be a significant indicator of hallucinogenic potency for 4-substituted phenylisopropylamines, Domelsmith et al.[6] have commented that these agents can be divided into two basic categories, inactive (or relatively inactive) compounds that lack a lipophilic 4-substituent and several highly active compounds that possess such a substituent. Thus, it was of interest (a) to compare the 5-HT receptor affinities and behavioral properties of several derivatives of 2,5-DMA that vary only with respect to their 4-position substituent and (b) to determine if a relationship exists between the human hallucinogenic potency of these agents (where data are available) and either their 5-HT receptor affinity or their activity in a drug discrimination paradigm, in which animals are trained to detect either the presence or absence of DOM-like behavioral effects.

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Chemistry. 2-Fluorohydroquinone, prepared by the Elbs persulfate oxidation of 2-fluorophenol as described by Feiring and Sheppard,[9] was methylated (Me_2SO_4) to afford 2,5-dimethoxyfluorobenzene (**6c**). Formylation of **6c** to the aldehyde **6b** was accomplished with α,α-dichlorodimethyl ether under Friedel–Crafts conditions; evidence for formylation para to the fluoro group is derived from examination of the ^1H NMR spectrum of **6b**, which reveals two aromatic proton signals that appear as singlets and integrate for one proton each. The aldehyde **6b** was converted to the nitropropene **6a** and reduced to **6** by means of $LiAlH_4$ in ether. Coutts and Malicky have previously reported the synthesis of the iodo derivative **8** by subjecting 1-(2,5-dimethoxy-4-aminophenyl)-2-acylamino)propane to a Sandmeyer reaction, followed by hydrolysis.[10] It was found that direct iodination of the *N*-acetyl derivative of 2,5-DMA (**1**) was possible if silver trifluoroacetate and I_2 were used; hydrolysis of the acetyl group afforded **8**. The nitro derivatives (±)-**9** and (*R*)-(−)-**9** were prepared by direct nitration of (±)-2,5-DMA (**1**) or its *R*(−) isomer. We have previously reported the synthesis of the positional isomer of (±)-DOB, i.e., **14**.[11]

Results and Discussion

The serotonin (5-HT) receptor affinities (pA_2 values) of compounds **1–9** are shown in Table I; all compounds were found to interact in a competitive manner as determined by the slopes of their Schild plots. With respect to the behavioral (discriminative stimulus) study, generalization was found to occur between racemic DOM and compounds **1–9** (Table I). That is, all of the compounds in Table I are capable of producing behavioral (discriminative) effects in rats similar to those produced by the training dose of racemic DOM. Compounds in Table II do not result in stimulus generalization (i.e., they produce stimulus effects that apparently differ from those produced by racemic DOM). Response rates, under drug and nondrug (saline) conditions, were not significantly different, except where complete disruption of behavior (no responding) occurred.

Receptor Affinity Study. Of the six isomeric dimethoxyphenylisopropylamines, high 5-HT receptor affinity is associated with a 2,5-dimethoxy pattern. Variation of the 4-position substituent within the series of 2,5-DMA analogues appears to further modulate affinity, but it does so over a relatively narrow (less than tenfold) range. Previous attempts to determine the role of the 4-position substituent on biological activity have been limited to the study of alkyl-substituted derivatives[2] or have included a large group of compounds with widely varying substitution patterns,[7] wherein the role of the 4-position substituent might have been masked. With respect to aromatic substituents, compounds **1–9** vary only at the 4-position. Examination of the pA_2 values for the nitro and iodo derivatives, **9** and **8**, respectively (whose 4-position substituents represent the extremes of the range of substituent-group π values[12] used in this study, i.e., $\pi_{NO_2} = -0.28$, $\pi_I = 1.12$), reveal less than a threefold difference in affinity, while the affinity of the fluoro derivative **6** ($\pi_F = 0.14$) is comparable to that of DOM ($\pi_{Me} = 0.56$) and DOET ($\pi_{Et} = 1.02$). These results suggest that the lipophilic nature of the 4-position substituent plays a minimal role in determining 5-HT receptor affinity and support our previous suggestion to this effect.[6] Nevertheless, such considerations cannot be completely ruled out because the effect of substituent lipophilicities may be overshadowed by the presence of a 2,5-dimethoxy pattern that, in itself, imparts substantial receptor affinity. The 4-position substituents differ not only in their lipophilic character but also with respect to, for example, their electronic and steric contribution. However, a detailed analysis of such effects is not warranted on the basis of the limited number of compounds examined and the narrow range of observed affinities.

Behavioral Studies. The discriminative stimulus paradigm is a useful tool for determing whether a group of agents is capable of producing similar behavioral effects (interoceptive cues) in animals.[13,14] This paradigm is a very specific indicator of drug-induced similarities between challenge compounds as compared to a standard agent. In brief, rats, trained to discriminate the central effects of 1.0 mg/kg of racemic DOM from saline in a two-lever operant chamber,[15] were challenged with agents **1–9**. Generalization ("transfer") is said to occur when a challenge compound results in the animals' responding >75–80% on the "DOM-appropriate" lever. That is, when generalization occurs, the animals apparently recognize the stimulus effects of a challenge drug as being similar to those of the training drug [i.e., in this case, 1.0 mg/kg of (±)-DOM]. As such, this procedure allows for both a qualitative and quantitative comparison within the series of agents under study. All of the compounds in Table I produce stimulus generalization when administered to the DOM-trained animals. Table I also shows that the *R*(−) isomers of DOB, DOI, and DON [(−)-**7** to (−)-**9**, respectively] are more active than their racemates. These results parallel our earlier findings that the *R*(−) isomers of 2,5-DMA, DOM, and DOET are several times more active than their *S*(+) enantiomers,[20] as well as the results of a study by Silverman and Ho, who have reported that (*R*)-(−)-DOM is more active than (*S*)-(+)-DOM when administered to (±)-DOM-trained animals.[16]

Correlations with Human Activity. We have previously suggested that the hallucinogenic potency of certain substituted phenylisopropylamines may be a consequence of, or related to, their affinity for 5-HT receptors.[11] Human hallucinogenic data exist for nine of the compounds in Table I [however, pA_2 data are only available for eight; (*R*)-(−)-DOB produces an agonistic response that precludes determination of a reliable pA_2 value[17]], and a relationship appears to exist between human potency and 5-HT receptor affinity (Figure 1). We have previously reported pA_2 values for six other phenylisopropylamines for which human data are available;[11,18] these agents are also included in Figure 1. It might be noted that only compounds with pA_2 values greater than 6.0 have been included in Figure

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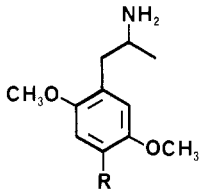
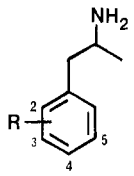
Table I. Receptor Affinity and Behavioral Data



compd	R	pA_2[a]	slope[b]	N[c]	dose, mg/kg	N[d]	% DOM-appropriate responding (± SEM)[a]	ED_{50},[f] mg/kg	human hallucinogenic potency[g]
(±)-1	H	6.83						5.51 (3.98-7.63)[h]	50
(±)-2	OMe	6.81			3.0	6/6	20 (11.4)	3.59 (2.85-4.51)	20
					3.5	5/5	59 (19.4)		
					4.0	5/5	70 (17.4)		
					5.0	5/6	81 (8.8)		
					5.5	6/6	90 (7.2)		
(±)-3	OEt	6.78 (±0.21)	1.08 (±0.45)	4	2.0	5/5	2 (1.2)	6.33 (4.34-9.22)	30
					5.0	5/5	16 (8.1)		
					8.0	5/5	68 (13.8)		
					9.0	4/5	85 (6.9)		
					10.0	1/5	*i*		
(±)-4	Me	7.13 (±0.13)[j]	0.92 (±0.12)	5				0.44 (0.29-0.68)[h]	2-5
(±)-5	Et	7.18			0.125	5/5	10 (4.0)	0.23 (0.14-0.39)	1.5-4
					0.25	5/5	44 (17.7)		
					0.50	5/5	99 (0.8)		
(±)-6	F	7.20 (±0.20)	0.93 (±0.29)	6	0.5	5/5	6 (3.8)	1.45 (0.95-2.20)	
					0.75	5/5	25 (19.0)		
					1.0	5/5	43 (8.4)		
					1.5	6/6	45 (10.0)		
					2.5	5/5	66 (10.5)		
					3.0	6/6	88 (5.5)		
(±)-7	Br	7.35			0.125	5/5	18 (12.0)	0.20 (0.13-0.32)	0.8-2.0
					0.20	5/5	51 (14.0)		
					0.25	5/5	70 (8.0)		
					0.50	5/5	91 (5.6)		
(−)-7	Br				0.10	5/5	47 (16.9)	0.10 (0.07-0.16)	0.4-1.0
					0.15	5/5	79 (8.8)		
					0.20	5/5	91 (3.7)		
(+)-7	Br	6.93			0.50	5/5	20 (13.0)	0.81 (0.55-1.20)	4-10
					0.75	5/5	35 (21.6)		
					1.50	5/5	96 (2.9)		
(±)-8	I	7.49 (±0.19)	1.13 (±0.33)	3	0.25	5/5	31 (14.6)	0.42 (0.25-0.71)	0.8-2.0
					0.50	5/5	41 (13.8)		
					0.75	5/5	80 (19.9)		
					1.00	5/5	93 (2.4)		
(−)-8	I	7.63 (±0.27)	1.01 (±0.19)	4	0.125	5/5	18 (10.4)	0.26 (0.15-0.44)	
					0.25	5/5	47 (19.8)		
					0.50	5/5	75 (19.8)		
					0.75	5/5	96 (3.8)		
(±)-9	NO_2	7.07 (±0.47)	0.81 (±0.18)	3	0.5	5/5	32 (17.6)	0.76 (0.44-1.30)	
					1.0	4/5	55 (14.5)		
					1.5	5/5	87 (6.0)		
(−)-9	NO_2	7.49 (±0.26)	0.93 (±0.14)	4	0.5	5/5	44 (10.2)	0.57 (0.38-0.85)	
					0.75	5/5	61 (18.2)		
					1.0	5/5	93 (6.5)		
saline (1 mL/kg)							5 (2.3)		

[a] pA_2 value followed by standard deviation. Values for (±)-1, (±)-2, (±)-5, and 7 have been previously reported[11] and are included for comparative purposes. [b] Negative slope of Schild plot followed by standard deviation. [c] Number of pA_2 determinations, using four to six dose-response curves for 5-HT for each pA_2 determination. [d] Number of animals responding/number of animals tested. [e] Data obtained during 2.5-min extinction session. Response rates, except where disruption of behavior occurred, were not significantly different under drug of nondrug (saline) conditions. [f] ED_{50} followed by 95% confidence limits. [g] Total dose in milligrams.[1] [h] ED_{50} for (±)-1 and (±)-4 have been previously reported.[15,20] [i] Disruption of behavior at this dose; no responding. [j] Represents data from previously reported pA_2[8] plus three new determinations.

Table II. Receptor Affinity and Behavioral Data for Several Miscellaneous Derivatives of 1-Phenyl-2-aminopropane



compd	R	dose, mg/kg	N^a	% DOM-appropriate responding (± SEM)[b]	pA_2[c]
(±)-10	H	1.0	5/5	2 (1.9)	5.27
		1.5	3/5	26 (8.4)	
		2.0	1/5	*d*	
		3.0	0/5	*d*	
(±)-11	2-OMe	2.0	5/5	2 (1.9)	5.54
		3.0	4/5	7 (4.7)	
		4.0	2/5	*d*	
(±)-12	3-OMe	2.0	5/5	8 (5.3)	5.93
		4.0	3/5	10 (2.3)	
		5.0	1/5	*d*	
(±)-13	4-OMe	0.5	5/5	13 (2.0)	5.15
		1.0	4/5	15 (1.8)	
		1.5	2/5	*d*	
(−)-13	4-OMe	0.5	5/5	18 (2.8)	5.38
		1.0	3/5	20 (4.6)	
		1.5	1/5	*d*	
(±)-14	2,5-$(OMe)_2$, 3-Br	1.0	5/5	2 (1.9)	5.27
		2.0	5/5	3 (2.1)	
		3.0	4/5	0	

[a] Number of animals responding/number of animals tested. [b] Data obtained during 2.5-min extinction session. [c] pA_2 values from ref 11. [d] Disruption of behavior.

1 on the basis that the mechanism of action, and, indeed, the behavioral effects, of agents with lower affinities, such as the psychoactive PMA (**13**), might differ from those with higher affinities. In as much as phenylisopropylamines at the lower end of the affinity scale might be capable of producing behavioral effects that differ from those at the higher end (e.g., from those of DOM), several such derivatives were administered to the DOM-trained animals (Table II). Administration of racemic amphetamine (**10**) does not result in generalization at doses of 1.0 and 1.5 mg/kg, while doses of 2.0 and 3.0 mg/kg produce complete disruption of behavior (i.e., no responding). These results are consistent with those reported by Silverman and Ho,[16] who found that generalization does not occur upon administration of (+)-amphetamine to DOM-trained rats. The 2-, 3-, and 4-methoxy derivatives (**11–13**, respectively), as well as the *R*(−) isomer of PMA [(−)-**13**], produce similar results, that is, no generalization at low doses and disruption of behavior at higher doses. The 3-positional isomer of DOB (i.e., **14**) produces saline-like responding at all doses tested. Thus, these compounds do not produce DOM-like behavioral (discriminative) properties and should not be included in comparisons of activity and 5-HT receptor affinity. Two remaining compounds, which we have previously reported to possess 5-HT receptor affinities comparable to that of DOM (**4**), are DOTB (pA_2 = 7.22) and DOAM (pA_2 = 7.02).[18] Complete DOM-stimulus generalization does not occur upon administration of either of these agents; thus, they too appear to produce an effect that differs from that produced by DOM and, as a consequence, are not included in Figure 1. Thus, for 14 phenylisopropylamines, there is excellent agreement[19]

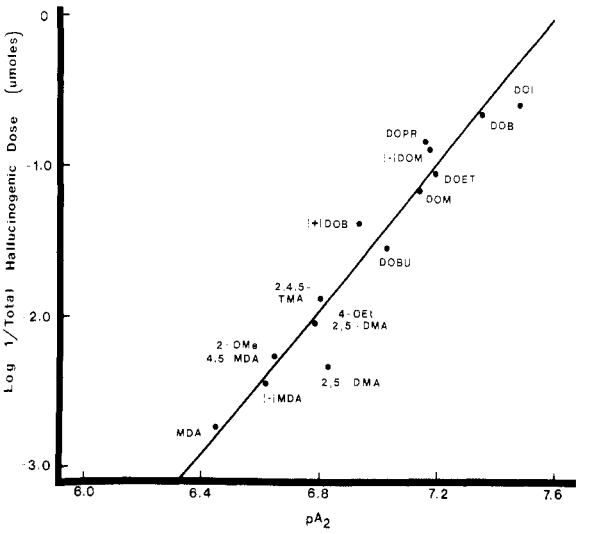


Figure 1. Plot of human hallucinogenic potency vs. serotonin receptor affinity (pA_2). Total human hallucinogenic doses (in milligrams) are from Table I, except for (*R*)-(−)-DOM (1–2.5 mg), (±)-DOPR (2–5 mg), (±)-DOBU (10 mg), (±)-2-OMe-4,5-MDA (30–50 mg), (±)-MDA (100–125 mg), and (*R*)-(−)-MDA (40–70 mg);[1] where dose ranges are given, the arithmetic mean was used.

between activity and affinity. Those agents, which are most potent in man, possess the highest 5-HT receptor affinities. It must be emphasized, however, that the reverse of this statement does not necessarily apply; that is, based on the affinities of DOTB and DOAM, it cannot be concluded that all compounds with a significant 5-HT receptor affinity will necessarily produce DOM-like effects in animals and/or hallucinogenic effects in man.

Since the hallucinogenic response in man is a subjective phenomenon, the meaningfulness of a correlation between human dose and a particular biological property or physicochemical parameter, regardless of the statistical significance of the correlation, is still a matter for discussion. Nevertheless, the above relationship strongly supports the contention that the neurotransmitter serotonin plays a role in the mechanism of action of these hallucinogenic agents.

Is the discriminative stimulus paradigm a suitable model for studying these hallucinogenic agents? Generalization experiments, using this behavioral procedure, are based on the hypothesis that drugs that produce similar subjective effects in humans will have similar discriminative stimulus properties in animals.[13c] Although the exact nature of the stimulus cues produced by these agents, as perceived by the animals, is unknown, this hypothesis has, nevertheless, received considerable suport.[13] With respect to this present study, Figure 2 is a plot of human hallucinogenic potency vs. activity (ED_{50} value) in the discriminative stimulus paradigm for the nine compounds in Table I for which human data are available; also shown are five additional compounds for which we have already published ED_{50} values.[20] Even though certain of these agents (e.g., DOI,[1] DOPR,[2] and DOBU[2]) have not been extensively investigated in man, there appears to be a good quantitative agreement between human hallucinogenic potency and generalization dose (ED_{50} value) for those agents where

(19) Correlation equation: log 1/total human hallucinogenic dose (micromoles) = 2.33 (±0.04) pA_2 − 17.81 (±1.90). N = 14, standard deviation = 0.21, r^2 (variance) = 0.92, F = 141.1, p < 0.001.

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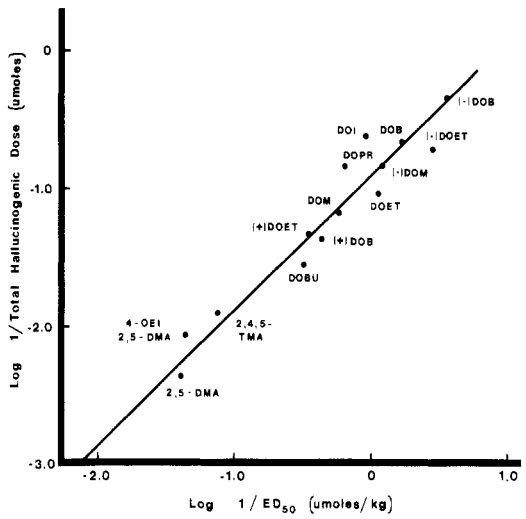

Figure 2. Plot of human hallucinogenic potency vs. drug-discrimination ED_{50} value, with DOM-trained animals. Total human hallucinogenic doses (in milligrams) are from Table I and Figure 1, except for (*R*)-(−)-DOET (0.75–2.0 mg) and (*S*)-(+)-DOET (3–8 mg). Because Snyder et al.[29] have reported that (*R*)-(−)-DOET is twice as active and (*S*)-(+)-DOET is half as active as racemic DOET, one-half and twice the Table I value for (±)-DOET was used for (*R*)-(−)-DOET and (*S*)-(+)-DOET, respectively.

DOM-stimulus generalization occurred.[21] One of the problems associated with the formulation of structure–activity relationships (SAR) for the phenylisopropylamine hallucinogens has been a lack of knowledge concerning commonality (i.e., similarity) of effect; inclusion, in attempted SAR correlations, of derivatives that produce dissimilar effects might lead to erroneous conclusions. Martin and Sloan, for example, have attempted to classify various hallucinogenic agents on their ability to produce an LSD-like effect.[22] It appears that the discriminative stimulus paradigm may also prove to be a useful tool for studying the mechanism of action of hallucinogenic agents by allowing their classification as to whether or not they produce DOM-like effects. The results of the affinity studies implicate 5-HT as playing a mechanistic role; the recent findings that the behavioral effects of (±)-DOM (4) can be effectively attenuated by pretreatment of the animals with central 5-HT antagonists, such as cinanserin,[16,23] methylsergide,[16] and pizotyline,[15] but not with the peripheral 5-HT antagonist xylamidine[16] or the dopamine antagonists chlorpromazine[23] and haloperidol,[16,23] lend further support to this hypothesis and suggest that these hallucinogenic agents might be acting in an agonistic manner at central 5-HT sites.

In summary, it appears that 2,5-dimethoxy substitution of phenylisopropylamines is important for high 5-HT receptor affinity; however, even this pattern is sensitive to the presence of other substituents (note the 100-fold difference in affinity between racemic **7** and its isomeric 3-bromo derivative **14**[11]). Substituents at the 4-position of the 2,5-DMA molecule apparently modulate affinity over a very narrow range; the contributional role of these substituents is unclear, although their lipophilic character seems to have only a minimal effect on affinity. Those agents that are most potent in man possess the highest 5-HT receptor affinities; however, a high receptor affinity doesn't appear to be sufficient to endow a compound with DOM-like properties.

(21) Correlation equation: log 1/total human hallucinogenic dose (micromoles) = 0.90 (±0.01) log 1/ED_{50} (micromoles/kilogram) −0.93 (±0.05). N = 14, standard deviation = 0.17, r^2 (variance) = 0.93, F = 155.1, $p < 0.001$.

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Experimental Section

Melting points were determined in open capillaries and are uncorrected. Infrared spectra were recorded on a Beckman Acculab 2 spectrophotometer as Nujol mulls. Nuclear magnetic resonance spectra were measured on a Varian 390, 100-MHz spectrometer in $CDCl_3$, and chemical shifts are reported as δ values in parts per million (ppm) downfield from tetramethylsilane as an internal standard. Optical rotations were obtained on an electronically balanced Perkin-Elmer 141 polarimeter, with a 1-dm cell, and concentrations of 2%.

(±)-1-(2,5-Dimethoxy-4-fluorophenyl)-2-aminopropane Hydrochloride (6). To a stirred and cooled (ice bath) mixture of $LiAlH_4$ (28 g, 0.7 mol) in dry Et_2O (600 mL) was added gradually a solution of **6a** (36.2 g, 0.15 mol) in THF (250 mL). After the addition, the mixture was stirred at room temperature for 1.5 h, heated at reflux for 15 min before cooling, and hydrolyzed with 28 mL of H_2O, followed by 25 mL of 2 N NaOH and then 75 mL of additional H_2O. After the inorganic precipitate was removed by filtration, the Et_2O–THF was evaporated in vacuo to a residual oil, which was further dried by four evaporations with 15- to 20-mL portions of dry C_6H_6. The oil was taken up in dry Et_2O and treated with sufficient ethereal HCl to give a distinctly acid reaction to moist pH paper. The colorless precipitated hydrochloride was collected and washed thoroughly with dry Et_2O: yield 32.5 g (87%); mp 160–162 °C. Recrystallization from Et_2O–EtOAc–EtOH afforded 30.8 g (82%) of **6**, mp 166–167 °C. Anal. ($C_{11}H_{17}ClFNO_2$) C, H, F. N.

1-(2,5-Dimethoxy-4-fluorophenyl)-2-nitropropene (6a). A mixture of 2,5-dimethoxy-4-fluorobenzaldehyde (41.3 g, 0.219 mol), NH_4OAc (4 g), and 110 mL of $C_2H_5NO_2$ was heated at reflux for 4 h and allowed to cool to room temperature. The solid product deposited was collected: yield 35.2 g of yellow prisms, mp 128–129 °C, and a second crop of 11.6 g, mp 127–128 °C, to give a total yield of 88.5%. The analytical sample was recrystallized from EtOH as yellow needles: mp 128–129 °C; NMR δ 6.92 (s, 1 H), 7.20 (s, 1 H) (para aromatic protons). Anal. ($C_{11}H_{12}FNO_4$) C, H, N.

2,5-Dimethoxy-4-fluorobenzaldehyde (6b). A solution of 2,5-dimethoxyfluorobenzene (40.7 g, 0.26 mol) in CH_2Cl_2 (215 mL) was cooled in an ice bath to 5–6 °C. Under vigorous stirring, 135 g (0.52 mol) of $SnCl_4$ was added, followed by the dropwise addition of dichloromethyl methyl ether (26 g, 0.27 mol) at a rate which maintained the internal temperature below 10 °C. The reaction mixture was allowed to warm to room temperature during 30 min with continued stirring and then was poured into a mixture of 500 g of ice and 75 mL of concentrated HCl, and the green solution was stirred for 1.5 h. The CH_2Cl_2 layer was separated and washed with 2 × 100 mL of 10% HCl, H_2O, 10% NaOH, H_2O, and finally with saturated brine. After the CH_2Cl_2 layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated, the residue was recrystallized from EtOH containing a small quantity of H_2O to yield 41.8 g (87.5%) of 2,5-dimethoxy-4-fluorobenzaldehyde (**6b**), mp 99–100 °C, 2,4-dinitrophenylhydrazone, mp 219–220 °C: NMR δ 6.32 (s, 1 H), 6.35 (s, 1 H) (para aromatic protons). Anal. ($C_9H_9FO_3$) C, H, F.

2,5-Dimethoxyfluorobenzene (6c). 2-Fluorohydroquinone was prepared by the Elbs persulfate oxidation of 2-fluorophenol as described by Feiring and Sheppard.[9] To a mechanically stirred solution of the crude hydroquinone (48.9 g, 0.3 mol) in 90 mL of EtOH was added 220 g (1.74 mol) of Me_2SO_4, and the mixture was cooled in an ice bath. A solution of NaOH (75 g, 1.88 mol) in H_2O (155 mL) was added at such a rate that the internal temperature remained at 20–30 °C. Following the addition, the stirred mixture was heated to 65–70 °C for 0.5 h and then cooled and extracted twice with Et_2O. The combined extracts were washed with H_2O, dried (anhydrous $MgSO_4$), and filtered. Evaporation of the solvent gave an oily residue, which was distilled in vacuo to yield 29 g of pure 2,5-dimethoxyfluorobenzene, bp 119–121 °C (40 mm) (44%, based on 2-fluorophenol not re-

covered). Anal. ($C_8H_9FO_2$) C, H, F.

(±)-1-(2,5-Dimethoxy-4-iodophenyl)-2-aminopropane Hydrochloride [(±)-8]. Compound (**8a**) was hydrolyzed in the manner described by Coutts and Malicky[10] to give the title compound in 71% yield, mp 196 °C (lit.[10] mp 198–200 °C) after two recrystallizations from EtOH–Et_2O.

(±)-*N*-Acetyl-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (8a). To a stirred mixture of 4.42 g (0.02 mol) of silver trifluoroacetate[24] and (±)-*N*-acetyl-1-(2,5-dimethoxyphenyl)-2-aminopropane[2] (4.74 g, 0.02 mol) in $CHCl_3$ (5 mL) was added dropwise, over a 2-h period, a solution of I_2 (5.08 g, 0.02 mol) in $CHCl_3$ (65 mL). After the mixture was stirred for 18 h, the precipitated AgI was removed by filtration. The filtrate was washed with aqueous $NaHSO_3$ and H_2O and dried over anhydrous $MgSO_4$. Evaporation of the $CHCl_3$ yielded 5.5 g of a brown residue, which was recrystallized from boiling EtOH–H_2O to give 2.21 g of the title compound, mp 162–163 °C (lit.[10] mp 165–166 °C).

(*R*)-(−)-1-(2,5-Dimethoxy-4-iodophenyl)-2-aminopropane Hydrochloride [(−)-8]. By the same procedures for (±)-**8**, 13 g (0.056 mol) of (*R*)-(−)-1-(2,5-dimethoxyphenyl)-2-aminopropane hydrochloride[25] [$[\alpha]^{25}_D$ −18.7° (H_2O)] was converted to 10.7 g (81%) of the *N*-acetyl derivative, mp 106–107 °C; iodination with 11.5 g (0.045 mol) of I_2 and 10 g (0.045 mol) of silver trifluoroacetate in 150 mL of $CHCl_3$ gave 4.7 g (31%) of (*R*)-(+)-*N*-acetyl-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane: mp 184–185 °C; $[\alpha]^{23}_D$ +9.6° (MeOH). Hydrolysis with NaOH,[10] followed by acidification, afforded 2.93 g (74%) of the title compound: mp 218–219 °C; $[\alpha]^{23}_D$ −12.0° (H_2O). Anal. ($C_{11}H_{17}ClINO_2$) N.

(*R*)-(−)-1-(2,5-Dimethoxy-4-nitrophenyl)-2-aminopropane Hydrochloride [(−)-9]. To an aqueous solution of 10 g (0.043 mol) of (*R*)-(−)-1-(2,5-dimethoxyphenyl)-2-aminopropane hydrochloride[25] was added an excess of 5 N NaOH. The liberated free base was taken up in C_6H_6–Et_2O, dried (anhydrous $MgSO)_4$, and filtered. Removal of the solvents in vacuo yielded a colorless oil, which was dissolved in 40 mL of HOAc. This solution was added dropwise during 0.5 h to 43 mL of 50% HNO_3 (*d* 1.13), and the mixture was stirred and kept at 0–5 °C. The resulting clear solution was poured over ice, made alkaline with 50% NaOH, and extracted with C_6H_6–Et_2O. Evaporation of the solvent gave a residue, which was dissolved in dilute HCl, and this solution was evaporated in vacuo to a nearly colorless solid residue. Recrystallization from EtOH–Et_2O gave 10.5 g (88%) of product: mp 231–232 °C dec; $[\alpha]^{23}_D$ −12.5° (H_2O). Anal. ($C_{11}H_{17}ClN_2O_4$) C, H, Cl, N. We prepared the racemic (±)-**9** by direct nitration of (±)-**1**, using the above method, mp (HCl salt) 207–209 °C (lit.[10] mp 203–204 °C).

Compounds (±)-**1**, (±)-**2**, (±)-**4**, (±)-**5**, and **7** were gifts from the NIDA, while (±)-**3** was available from a previous study.

Affinity Assay. Male Sprague–Dawley rats (200–250 g) were used in this study. The fundus preparation employed was essentially that of Vane,[26] with the previously described modifications.[8,11] Cumulative dose–response curves were obtained, after a 1-h equilibration period, for serotonin oxalate (7–10 increasing concentrations) both in the absence and in the presence of increasing concentrations of test compound. At least four to five dose–response curves were obtained for each pA_2 determination and at least triplicate pA_2 values were obtained (Table I). Certain compounds, notably (±)-**4**, (−)-**8** and (−)-**9**, produced an agonistic response at the highest concentrations tested; when this occurred, the crest of this response was used as the new base line. The interaction of test compound with 5-HT receptors was assumed to be competitive when Schild plot slopes were between −0.8 and −1.2.

Behavioral Assay. The drug discrimination training procedure for these animals has been reported previously.[15] Specfically, 30 male Sprague–Dawley rats were trained to discriminate racemic DOM (1.0 mg/kg) from saline in a two-lever operant task. In this procedure, the administration of saline or DOM, 15 min prior to a variable-interval, 15-s (VI-15 s) schedule of reinforcement, served as the discriminative cue for the correct (reinforced) lever. Occasional periods (2.5 min) of nonreinforcement were used to assess the degree of stimulus control exerted over behavior by saline and DOM and to evaluate the 4-substituted derivatives of 2,5-DMA. For those compounds where generalization (transfer, substitution) occurred, ED_{50} values were determined from the dose–response data by the method of Litchfield and Wilcoxin.[27] (For a discussion of the use of the ED_{50} value as it relates to classification of drugs on the basis of their discriminative stimulus characteristics in rats, see Barry.[28]) These ED_{50} values are the calculated doses at which the rats perform 50% appropriate drug-lever responding.

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Potential Histamine H_2-Receptor Antagonists.[1] 4. Benzylhistamines

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As part of our studies aimed at designing histamine H_2-receptor antagonists, the effect on histaminergic activity of introducing benzyl substituents at various positions in the histamine molecule is described. New synthetic methods are reported for the novel 4-benzyl-, β-benzyl- and 4,N^τ-dibenylhistamines and the reported 2-benzylhistamine. The novel N^τ-benzylhistamine was synthesized by the versatile route reported by us for the synthesis of N^τ-methylhistamine. These benzylhistamines, together with the reported N^α- and N^π-benzylhistamines, were tested for agonist and antagonist activity at both H_1 and H_2 receptors. The results obtained indicate that introduction of a benzyl group into the histamine molecule causes a marked reduction in H_1- or H_2-agonist activity, and none of the compounds showed consistent antagonist activity. Evidently, the sterically demanding benzyl substituent is not easily accommodated in the agonist binding mode and is unable to locate a lipophilic receptor region for potential hydrophobic binding.

The discovery of the selective antagonist burimamide has permitted the characterization of histamine H_2 receptors and furnished a class of drugs with a completely novel pharmacological action.[2] Chemical modification of

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