(50%) of **9** as an oil: IR (neat) 1705 (cyclopentenone CO), 1638 and 1590 cm^{-1} (C=C); NMR ($CDCl_3$) δ 1.15 (3 H, s, CH_3-5), 2.40 and 2.90 (2 H, AB q, J = 19 Hz, each peak is split into J = 2.5 Hz, CH_2-4), 4.23 (2 H, s, CH_2O), 6.25 (1 H, m, H-2), 6.36 (1 H, d, J = 17.0 Hz, COC*H*=CHPh), 7.70 (1 H, d, J = 17.0 Hz, COCH=C*H*PH), 7.40 (5 H, m, aromatic protons), and 7.75 (1 H, overlapped m, H-3).

5-Methyl-5-(3,4,5-trimethoxybenzoyl)oxymethyl-2-cyclopentenone (10). A mixture of 5-methyl-5-hydroxymethyl-2-cyclopentenone (**7**, 0.4 g, 3.2 mmol) and 3,4,5-trimethoxybenzoyl chloride (1.1 g, 4.3 mmol) in dry $CHCl_3$ (30 mL) and pyridine (3 mL) was allowed to stand at room temperature overnight. The reaction mixture was worked up in an analogous manner as described for the preparation of **9**. The viscous material was purified by preparative TLC [silica gel, benzene–EtOAc (4:1)] to furnish 0.5 g (49%) of **10**: mp 83–85 °C (Et_2O–petroleum ether); IR ($CHCl_3$) 1715 (cyclopentenone CO) and 1600 cm^{-1} (aromatic ring); NMR ($CDCl_3$) δ 1.23 (3 H, s, CH_3-5), 2.52 and 2.96 (2 H, AB q, J = 19 Hz, each peak is split into J = 2.5 Hz, CH_2-4), 3.90, 3.91, and 3.92 (9 H, 3 s, $3OCH_3$), 4.32 (2 H, s, CH_2O), 6.30 (1 H, m, H-2), 7.21 (2 H, s, aromatic protons), and 7.78 (1 H, m, H-3).

Bis(5-methyl-5-methylenyl-2-cyclopentenone)sebacate (11). A mixture of 5-methyl-5-hydroxymethyl-2-cyclopentenone (**7**, 0.517 g, 4.1 mmol) and sebacyl chloride (0.47 g, 2 mmol) in dry benzene (10 mL) and dry pyridine (1 mL) was allowed to stand at room temperature for 24 h. The mixture was worked up as in the preparation of **9**. The product was purified by preparative TLC [silica gel, Et_2O–hexane (4:1)] to yield 210 mg (25%) of **11**: oil; IR (CCl_4) 1740 (ester CO), 1715 (cyclopentenone CO), and 1595 cm^{-1} (C=C); NMR ($CDCl_3$) δ 1.13 (6 H, s, $2CH_3$), 4.06 (4 H, s, $2OCH_2$), 6.23 (2 H, m, COC*H*=CH), and 7.80 (2 H, m, COCH=C*H*).

5-Methyl-5-carbethoxy-2-bromocyclopentenone (12). A solution of Br_2 (1.92 g, 0.012 mol) in AcOH (2 mL) was added dropwise to a stirring ice-cold solution of 2-methyl-2-carbethoxycyclopentanone (**2**, 1.70 g, 0.01 mol) in HOAc (1 mL) and the mixture then stirred at room temperature overnight. The product was diluted with H_2O and extracted with Et_2O. The Et_2O extract was washed with 5% $NaHCO_3$ and H_2O, dried, and evaporated. Vacuum distillation of the oily residue gave 1.7 g (70%) of **12**: bp 110–124 °C (1.2 mm) [lit.[10] bp 128–131 °C (8 mm)].

5-Methyl-5-carbethoxy-2-cyclopentenone (13). 1,5-Diazabicyclo[5.4.0]undec-5-ene (0.9 g, 7.2 mmol) was added to a solution of 5-methyl-5-carbethoxy-2-bromocyclopentanone (**12**, 1.1 g, 4.8 mmol) in dry benzene (20 mL). The mixture was stirred at 90 °C (oil bath temperature) for 2 h. Upon cooling, 10% HCl (10 mL) was added and the product extracted with Et_2O. The extract was washed with H_2O, dried (Na_2SO_4), and evaporated. Chromatography of the residual oil on silica gel [10 g; Et_2O–hexane (1:3)] followed by distillation of the eluent gave 235 mg (29%) of **13**: bp 80–90 °C (3 mm) [lit.[10] bp 99–102 °C (10 mm)]; IR (neat) 1740 (ester CO), 1710 (cyclopentenone CO), and 1595 cm^{-1} (C=C); NMR ($CDCl_3$) δ 1.24 (3 H, t, J = 7.0 Hz, OCH_2CH_3), 1.44 (3 H, s, CH_3-5), 2.52 and 3.34 (2 H, AB q, J = 19 Hz, each peak is split into J = 2.5 Hz, CH_2-4), 4.20 (2 H, q, J = 7.0 Hz, OCH_2CH_3), 6.30 (1 H, m, H-2), and 7.92 (1 H, m, H-3).

Biological Methods. In vitro cytotoxicity was determined with H.Ep.-2 cells using the rapid microtiter technique of Huang.[11] A compound is considered active if it shows an $ED_{50} \leq 4$ μg/mL. In the in vivo Walker 256 ascites carcinosarcoma screen, 10^6 tumor cells were implanted ip into Sprague–Dawley male rats (~80 g). Test compounds were administered ip (2.5 mg/kg/day). T/C values were calculated. Melphalan was used as a positive standard.

In the P-388 lymphocytic leukemia screen, 10^6 cells (hemocytomete) were implanted ip into male DBA/2 mice (~20 g) on day 0. Test compounds were administered ip at 25 mg/kg/day for 2 weeks. T/C values were calculated from average survival times. 5-Fluorouracil was used as a positive standard.

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Serotonin Receptor Binding Affinities of Several Hallucinogenic Phenylalkylamine and *N,N*-Dimethyltryptamine Analogues

Richard A. Glennon,* Stephen M. Liebowitz, and Elizabeth C. Mack

Department of Pharmaceutical Chemistry, School of Pharmacy, Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia 23298. *Received February 9, 1978*

Hallucinogenic phenylalkylamine and *N,N*-dimethyltryptamine analogues are known to affect serotonergic systems both in vivo and in vitro. Using a rat stomach fundus model, the 5-HT receptor binding affinities of several of these analogues were determined and compared. The most behaviorally potent analogues examined, DOB, DOM, and 5-methoxy-*N,N*-dimethyltryptamine, were found to possess rather high affinities (pA_2 = 7.35, 7.12, and 7.08, respectively) for the 5-HT receptors of the model system.

Though the mechanism by which hallucinogenic tryptamine analogues produce their profound mental effects has yet to be elucidated, there is evidence that serotonin (5-hydroxytryptamine, 5-HT) receptors may play a pri-

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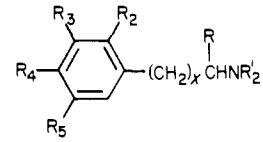
Table I. Binding Affinity Data[a]



no.	R_2	R_3	R_4	R_5	R	R'	x	pA_2[b]	n[c]
3	CH_3O	H	CH_3	CH_3O	CH_3	H	1	7.12 (±0.07)	2
4	CH_3O	H	Br	CH_3O	CH_3	H	1	7.35 (±0.08)	2
5	CH_3O	H	H	CH_3O	CH_3	H	1	6.83 (±0.09)	4
6	CH_3O	H	CH_3O	CH_3O	CH_3	H	1	6.81 (±0.08)	2
7	H	-OCH_2O-		H	CH_3	H	1	6.45 (±0.04)	2
8	CH_3O	H	H	CH_3O	H	H	1	6.85 (±0.19)	3
9	CH_3O	H	H	CH_3O	CH_3	CH_3	1	6.50 (±0.08)	2
10	CH_3O	H	H	CH_3O	H	CH_3	1	6.52 (±0.19)	3
11	CH_3O	H	H	CH_3O	H	CH_3	2	5.45 (±0.02)	2
12	H	CH_3O	CH_3O	CH_3O	H	H	1	5.65 (±0.10)	4
1	*N,N*-dimethyltryptamine							6.00 (±0.08)	2
2	5-methoxy-*N,N*-dimethyltryptamine							7.08 (±0.12)	3
13	7-methyl-*N,N*-dimethyltryptamine							6.29 (±0.08)	2

[a] 5-HT: pD_2 = 7.38 (±0.20), n = 22. [b] Values are ± standard deviation. [c] Number of determinations.

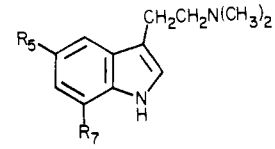
mary role. For example, Aghajanian and Haigler,[1] employing a microiontophoretic technique, have demonstrated that low doses of hallucinogenic tryptamines act preferentially upon presynaptic 5-HT receptors to inhibit raphe neurons. Bennett and Snyder[2,3] have investigated the binding of tryptamines to calf brain membrane preparations and have suggested that the binding sites involved might be postsynaptic 5-HT receptors. For additional evidence, see reviews by Brimblecombe and Pinder[4] and by Sankar.[5]

The nature of the hallucinogenic response is rather subjective, and therefore its measurement is necessarily qualitative. Alternative measures of biological activity might more accurately reflect the binding phenomena involved in the mechanism of action of various hallucinogens, if they parallel hallucinogenic activity. We have examined the binding affinities (pA_2 values) of *N,N*-dialkyltryptamines and related analogues for the 5-HT receptors of the isolated rat stomach fundus preparation with the expectation that an investigation of this binding might eventually serve as a model for other drug/5-HT receptor interactions of these hallucinogenic analogues.[6-8] Thus far, it appears that behaviorally active tryptamine analogues possess a relatively high affinity for the 5-HT receptors of this model system.[6,8]

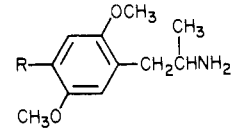
Recent evidence suggests that the hallucinogenic phenylalkylamines (i.e., analogues of amphetamine and mescaline) can also interact with the 5-HT receptors of various isolated tissue preparations and other model systems.[2,9-16] Furthermore, Nichols et al.[17] have suggested that the agonistic activity of phenylalkylamines on 5-HT receptors of isolated sheep umbilical artery preparations may, in part, be useful in predicting the hallucinogenic potency of such compounds in man. It would thus appear, if 5-HT receptor interactions are related to the activity of the phenylalkylamines, that they might possess binding characteristics similar to those of the tryptamines. This prompted us to determine the binding affinities of a small series of phenylalkylamines and to compare these with the affinities of *N,N*-dimethyltryptamine (DMT, 1) and 5-methoxy-*N,N*-dimethyltryptamine (5-OMe-DMT, 2).

Results and Discussion

The binding affinity data are reported in Table I. Antagonism appears to be competitive as noted by parallel dose–response curves in the absence and in the presence of increasing concentrations of compound. The pA_2 (7.08) determined for 5-OMe-DMT (2) is nearly identical with



1, R_5 = R_7 = H
2, R_5 = OCH_3; R_7 = H
13, R_5 = H; R_7 = CH_3



3, R = CH_3
4, R = Br

the value (7.10) we previously reported.[6] Of the phenylalkylamine analogues examined, 2-amino-1-(2,5-dimethoxy-4-methylphenyl)propane (DOM, 3) and DOB (4) possess the highest binding affinity. Removal of the 4-methyl group of 3 results in a twofold decrease in affinity (compound 5). Both 4-methoxylation (compound 6) and removal of the α-methyl group (compound 8) of 5, remarkably, have no effect on binding affinity. Amine dimethylation of both 5 and 8 results in an approximate twofold decrease in affinity (compounds 9 and 10, respectively). Extension of the side chain of 10 by one methylene unit also decreases affinity (compound 11). The 3,4,5-trisubstitution pattern of mescaline (12) results in a reduced affinity.

Various investigators have studied the agonistic effects of hallucinogens, including analogues of phenylisopropylamine,[9,11,15] on the rat fundus model. It has been difficult to decipher these data in light of the demonstration by Winter and Gessner[18] that this isolated tissue preparation possesses two distinct types of contractile tryptamine receptors, the 5-HT receptors and the PRT or phenoxybenzamine-resistant tryptamine receptors. Thus, a compound may produce a response by an agonistic interaction with either one or both types of receptors. Although investigations using this agonistic model might result in data which are difficult to interpret, determination of pA_2 values, by virtue of the manner in which they are obtained, circumvents this problem. It might be mentioned, however, that in this preparation the agonistic interaction of DOM is almost exclusively at the 5-HT receptors (unpublished data).

DOM (3) and DOB (4) are the most potent hallucinogens listed in Table I; thus, it is significant that they possess the highest affinities, of the compounds examined, for the 5-HT receptors of this model system. The actual affinity of the active isomers may be somewhat higher since the

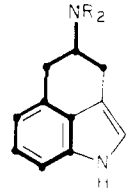


Figure 1. Phenylisopropylamine structure superimposed over tryptamine structure.

racemic mixtures were used in this study. α-Methylation, comparing compounds **5** and **8**, appears to have very little effect on binding affinity. Although the phenylisopropylamines are usually more potent hallucinogens than their phenethylamine counterparts,[4] the difference in activity between **5** and **8** is, in all likelihood, not directly related to their binding affinity as determined in this model system. Such differences in activity might be related, however, to the ability of the α-methyl group to impede metabolic oxidative deamination.[19] Substitution at the 4 position of these compounds also may enhance their in vivo activity by virtue of blocking their metabolism.[20] In addition to this effect, a methyl group at this position might also enhance binding to the receptor via a hydrophobic interaction. Using a sheep umbilical artery preparation, Nichols et al.[17] have found evidence for a hydrophobic region in the vicinity of the 4-position region of the binding site. Comparing the affinities of **3** and **5**, the rat fundus model may also possess a hydrophobic binding region. Examination of the agonistic activity of tryptamine analogues has led Johnson and Green[21] to make a similar suggestion using this same model system. If the phenylalkylamines and *N,N*-dimethyltryptamines are binding to the 5-HT receptors in an analogical manner, it should be possible to take advantage of this putative hydrophobic site to increase the binding affinity of DMT analogues. One way in which similar binding may occur is illustrated in Figure 1;[22] the 4 position of the phenylisopropylamines would be congruous to the 7 position of the DMT analogues. As shown in Table I, 7-methylation of DMT results in a twofold increase in affinity (compound **13**); this is similar to the difference in affinity between **3** and **5**.

Those compounds, in Table I, which are the most behaviorally active have relatively high binding affinities. *N,N*-Dimethylation of phenylalkylamines generally results in a decrease or abrogation of hallucinogenic activity.[4] Because the affinity of **9**, for example, is similar to or greater than that of two recognized hallucinogens, DMT (**1**) and MDA (**7**), it would appear that binding affinity may not be a singularly sufficient parameter to explain the potency of these compounds. It might be added, however, that there have been no reports on the human evaluation of **9** and that N-monomethylation of MDA (**7**) does result in a compound with psychotomimetic properties.[19]

Additional aspects of these interactions remain to be investigated, e.g., stereospecific binding and the effects of substitution pattern variation as well as further investigation of the hydrophobic region. Such studies are now in progress. However, the preliminary data demonstrate similar 5-HT receptor binding affinities for various analogues of two classes of hallucinogenic agents, namely, the phenylisopropylamines and the *N,N*-dialkyltryptamines. Several of the most potent agents, 5-OMe-DMT (**2**), DOM (**3**), and DOB (**4**), possess relatively high affinities for the 5-HT receptors of the model system used in this investigation.

The potencies of tryptamines in causing contractions of the fundus strip paralleled their potencies in blocking lysergic acid diethylamide (LSD) binding by rat brain homogenates; thus, the fundus strip appears to be a valid model for brain receptors.[23] In light of this demonstration, our findings bear additional significance. Although the 5-HT receptors of this model system possess characteristics which most resemble those of the postsynaptic calf-brain receptors reported by Bennett and Snyder,[2] the exact nature of these receptors is still unclear. A further investigation employing this model might help elucidate the binding phenomena involved in, and the structural requirements necessary for, this hallucinogen/5-HT receptor interaction.

Experimental Section

Nuclear magnetic resonance (^{1}H NMR) spectra were recorded using a Perkin-Elmer R-24 spectrometer with Me_4Si as an internal standard. Infrared spectra were obtained on a Perkin-Elmer 257 spectrophotometer. Elemental analyses were performed by Atlantic Microlab Inc., Atlanta, Ga. All melting points were determined on Thomas-Hoover melting point apparatus and are uncorrected. All of the compounds in Table I with the exception of mescaline sulfate are HCl salts except for the tryptamine derivatives which are hydrogen oxalate salts. Compounds **3**, **6**, and **7** were gifts from NIDA, while compound **8** was obtained from the Psychopharmacology Research Branch of NIMH. Compounds **5**,[24] **10**,[24] and **13**[25] were prepared according to literature procedures. Where the possibility of optical isomers exists, racemic mixtures were used.

(±)-2-(*N,N*-Dimethylamino)-1-(2,5-dimethoxyphenyl)propane Hydrochloride (9). At 10 °C, 2.5 mL of formaldehyde (40%) was added to a stirred solution of formic acid (97%, 2.2 mL) and 2-amino-1-(2,5-dimethoxyphenyl)propane[26] (2 g, 10.25 mmol). The reaction mixture was immersed into a preheated oil bath (90–100 °C) and heated until CO_2 began to evolve. At this time heating was discontinued until evolution of CO_2 ceased (20–30 min). The mixture was heated at 95–100 °C for 8 h, cooled, and acidified with 4 N HCl (5.5 mL). Solvent was removed under reduced pressure; the residue dissolved in H_2O (6 mL) and 4 mL of 18 N NaOH was added. After extraction with benzene (3 × 20 mL), the combined extracts were dried (Na_2SO_4) and the solvent was removed in vacuo to give a crude yellow oil. Distillation afforded 1.5 g (65%) of the amine, bp 97 °C (0.45 mm). The salt was prepared by addition of dry HCl to an Et_2O solution of the amine, to yield the desired product after recrystallization from EtOAc: mp 133–135 °C (lit.[27] mp 136 °C).

3-(2,5-Dimethoxyphenyl)propanol (14). Under an N_2 atmosphere, 2,5-dimethoxycinnamic acid (12.5 g, 60 mmol) was added in small portions to a stirred suspension of $LiAlH_4$ (3.5 g, 90 mmol) in 100 mL of THF at 0 °C. The reaction mixture was stirred at 0 °C for 2 h and refluxed for 1 h; excess $LiAlH_4$ was destroyed by the dropwise addition of 20% H_2O in THF at 0 °C. After the reaction mixture was filtered and the filtrate dried (Na_2SO_4), the solvent was removed in vacuo and the crude product distilled to yield 9.4 g (81%) of **14**, bp 113–115 °C (0.1 mm) [lit.[28] bp 105–108 °C (0.1 mm)].

3-(2,5-Dimethoxyphenyl)bromopropane (15). A solution of phosphorus tribromide (2.3 g, 8.5 mmol) in 20 mL of benzene was added dropwise to a stirred solution of **14** (4.9 g, 25 mmol) in an equal amount of benzene at 5 °C. The reaction mixture was stirred at 0–5 °C for 1 h and then at 60 °C for 3 h. The solution was allowed to cool; ice (10 g) was added and stirring continued for 30 min. The benzene portion was washed twice with H_2O (10 mL), dried (Na_2SO_4), and evaporated to dryness under reduced pressure. Distillation of the crude product gave 3.5 g (55%) of **15** as a clear colorless liquid, bp 102–103 °C (0.05 mm). Anal. ($C_{11}H_{15}BrO_2$) C, H, Br.

***N,N*-Dimethylamino-3-(2,5-dimethoxyphenyl)propane Hydrochloride (11).** A solution of **15** (2.07 g, 8 mmol) and dimethylamine (1.1 g, 24 mmol) in 25 mL of EtOH was heated in a Parr bomb (45-mL capacity) in an oil bath at 90–100 °C for 5 h. When cool, solvent was removed under reduced pressure and 10 mL of H_2O added. The mixture was shaken with 10 mL of 20% aqueous NaOH and extracted twice with 25-mL portions of Et_2O. The Et_2O fractions were combined, dried (Na_2SO_4), and evaporated to dryness under reduced pressure. Distillation yielded

1.46 g (82%) of the amine, bp 97–99 °C (0.06 mm). The HCl salt was prepared by bubbling HCl through an Et_2O solution of the amine at 0 °C. The salt was collected and precipitated from absolute EtOH by the dropwise addition of Et_2O to afford small white needles, mp 136–137 °C. Anal. ($C_{13}H_{21}NO_2$·HCl) C, H, N.

Binding Affinity Studies. Sprague–Dawley rats, of either sex, weighing 200–250 g (Flow Laboratories, Dublin, Va.) were used. The rat stomach fundus preparation employed was essentially that described by Vane[29] with the following modifications: (a) the bathing solution, kept at 37 °C, was that of Armitage and Vane;[30] (b) no hyoscine was added to the bathing solution; (c) responses were recorded on a smoked drum revolving at 3 mm/min using a pendular auxotonic lever[31] with a magnification of 8 and a resting load on the muscle of 1 g; (d) two strips were cut from the same tissue and used in parallel; (e) the relative sensitivity of the two strips was determined, after a 1-h equilibration period, by the use of 5-HT doses giving submaximal contractions. Only one compound was tested per preparation.

The ability, or potency, of each agent to inhibit the contractile response to 5-HT was determined by obtaining cumulative dose–response curves to 5-HT, first in the absence of the agent in question and, then, in the presence of increasing concentrations thereof. A minimum of five dose–response curves was generated per run. The ED_{50} of 5-HT was determined for each of these curves and the apparent affinities calculated as pA_2 values by the method of Arunlakshana and Schild.[32]

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Facile Syntheses of Potent Dopaminergic Agonists and Their Effects on Neurotransmitter Release

A. S. Horn,* C. J. Grol, D. Dijkstra,

Department of Pharmacy, University of Groningen, Groningen, The Netherlands

and A. H. Mulder

Department of Pharmacology, Free University, Amsterdam, The Netherlands. *Received February 17, 1978*

The facile syntheses of important intermediates used in the preparation of the two potent dopaminergic agonists, 2-amino-6,7-dihydroxytetrahydronaphthalene (11) (referred to by some authors as ADTN) and its 5,6-dihydroxyl isomer 12, are described. Thus 6,7-dimethoxy-2-tetralone has been prepared in two steps and 5,6-dimethoxy-2-tetralone in three steps both from commercially available materials. The effects of 11, 12, and the noncatechol analogue, 2-aminotetrahydronaphthalene (ATN), on radioactive neurotransmitter release have been studied in vitro using rat brain slices. It has been shown that both 11 and 12, at a concentration of 2 μM, cause a release of [^{3}H]-DA and NA, 11 being more potent than 12 in releasing [^{3}H]-DA. ATN (2 μM) was found to be inactive in these experiments which shows the importance of the catechol function in this uptake–release process.

Although L-Dopa is currently the drug of choice for the treatment of parkinsonism its use is complicated by various side effects and problems due to metabolic loss, and there is currently great interest in finding other possible dopamine (DA) receptor agonists.[1] Two DA analogues which have attracted attention in recent years are 2-amino-6,7-dihydroxytetrahydronaphthalene (11) (referred to by some authors as ADTN) and the isomeric 2-amino-5,6-dihydroxytetrahydronaphthalene (12). A variety of neurochemical, pharmacological, and behavioral evidence

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