1.89 (2.0). The TLC, paper electrophoresis, analytical HPLC, and FABMS data are given in Table III.

D-Tyr-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr-OH (8). The protected peptide resin to the title compound was prepared as reported for 1, except that a standard chloromethylated copoly(styrene–1% divinylbenzene) resin (vida supra, Merrifield resin) was used. The initial C-terminal amino acid N^{α}-Boc-Thr(*O*-Bzl) was attached to the resin by the method of Gisin[20] to give the resin substituted with Thr to the extent of about 0.40 mmol/g of resin. This resin was then used directly in the synthesis. The protected peptide resin corresponding to the title compound was obtained by stepwise coupling of the following N^{α}-Boc-protected amino acids (in order of addition): N^{α}-Boc-Cys(*S*-4-MeBzl); N^{α}-Boc-Thr(*O*-Bzl); N^{α}-Boc-Lys(N^{ϵ}-2-ClZ); N^{α}-Boc-D-Trp; N^{α}-Boc-Tyr(*O*-2-*BrZ*); N^{α}-Boc-Cys(*S*-4-MeBzl); N^{α}-Boc-D-Tyr(*O*-2-BrZ). After removal of the N^{α}-Boc protecting group and drying in vacuo there was obtained D-Tyr(*O*-2-BrZ)-Cys(*S*-4-MeBzl)-Tyr(*O*-2-BrZ)-D-Trp-Lys(N^{ϵ}-2-ClZ)-Thr(*O*-Bzl)-Cys(*S*-4-MeBzl)-Thr(*O*-Bzl)-*O*-resin. The peptide was cleaved from the resin and the protected groups removed in the usual manner using HF; the compound was cyclized and the title compound purified as reported in 1 to give 8 as a white powder: yield 9%. Amino acid anal.: Tyr, 1.94 (2.0); Lys, 0.93 (1.0); Thr, 1.84 (2.0). The TLC, paper electrophoresis, analytical HPLC, and FABMS data are given in Table III.

D-PhGly-Cys-Tyr-D-Trp-Lys-Thr-Pen-Thr-NH$_2$ (9). The protected peptide resin to the title compound was prepared as reported for 1, except that N^{α}-Boc-D-PhGly was used instead of N^{α}-Boc-D-Phe in the 1-position of the peptide in the coupling scheme to give D-PhGly-Cys(*S*-4-MeBzl)-Tyr(*O*-2-BrZ)-D-Trp-Lys(N^{ϵ}-2-ClZ)-Thr(*O*-Bzl)-Pen(*S*-4-MeBzl)-Thr(*O*-Bzl)-pMBHA resin. The cyclic peptide was obtained in a purified form by methods outlined for compound 1 to give 9 as a white powder: yield 10%. Amino acid anal.: Cys, 1.02 (1.0); Tyr, 1.06 (1.0); Thr, 1.86 (2.0); Lys, 0.94 (1.0). The TLC, paper electrophoresis, analytical HPLC, and FABMS data are given in Table III.

D-PhGly-Pen-Tyr-D-Trp-Lys-Thr-Cys-Thr-OH (10). The protected peptide resin to the title compound was prepared as above except that N^{α}-Boc-Pen(*S*-4-MeBzl) was used instead of N^{α}-Boc-Cys(*S*-4-MeBzl) in the 2-position and N^{α}-Boc-D-PhGly instead of N^{α}-Boc-D-Tyr(*O*-2-BrZ) in the 1-position to give D-PhGly-Pen(*S*-4-MeBzl)-Tyr(*O*-2-BrZ)-D-Trp-Lys(N^{ϵ}-2-ClZ)-Thr(*O*-Bzl)-Cys(*S*-4-MeBzl)-Thr(O-Bzl)-*O*-resin. The peptide was cleaved from the resin, the protecting groups removed, the peptide cyclized, and the title compound obtained in a highly purified form as outlined for 8 to give the product 10 as a white powder: yield 16%. Amino acid anal.: Tyr, 0.94 (1.0); Thr, 1.88 (2.0); Lys, 1.00 (1.0). The TLC, paper electrophoresis, analytical HPLC, and FABMS data are given in Table III.

Radioreceptor Assays. Adult Sprague-Dawley rats (150–200 g) were killed and the brains were rapidly removed and homogenized (10% w/v) in 0.32 M sucrose in a glass homogenizer with a motor-driven Teflon pestle. The homogenate was centrifuged at 1000*g* for 10 min, and the resulting pellet was resuspended in 50 mM Tris·HCl buffer (pH 7.4 at 25 °C) containing 5 mM $MgCl_2$, bovine serum albumin at 2 mg/mL, and bacitracin at 20 μg/mL by using a Polytron homogenizer (15 s, setting 5). The centrifugation and resuspension step was repeated once.

Rat brain plasma membranes (100 μL) were incubated at 25 °C for 120 min (180 min using [^{3}H]DPDPE) in a total volume of 1 mL of 50 mM Tris·HCl buffer (pH 7.4, as above) containing 0.2 nM [^{125}I]CGP23,996, 1 nM [^{3}H]naloxone, or [^{3}H]DPDPE and at least 10 freshly prepared concentrations of our synthetic somatostatin analogues. All incubations were done in duplicate using polypropylene test tubes, and every compound was tested at least three times. The concentration of test compounds was determined by quantitative amino acid analysis or from published molar extinction coefficients. Incubation was terminated by rapid filtration (Brendel M-24R cell harvester) of the incubation mixture through a GF/B glass fiber filter that had been pretreated with 0.1% polyethylenimine in order to reduce filter binding. Specific binding to somatotstatin or μ or δ opioid receptors was defined as the difference in the amounts of radioligands bound in the absence or presence of 1 μM somatostatin, 1 μM naltrexone, or 1 μM DPDPE, respectively. The data were analyzed by using nonlinear least-squares regression analysis on the Apple II+ computer. Programs were generously provided by SHM Research Corp., Tucson, AZ.

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5-HT$_1$ and 5-HT$_2$ Binding Characteristics of Some Quipazine Analogues

Richard A. Glennon,*† R. M. Slusher,† Robert A. Lyon,‡ Milt Titeler,‡ and J. D. McKenney†

Department of Medicinal Chemistry, School of Pharmacy, Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia 23298, and Department of Pharmacology, Albany Medical College, Albany, New York 12208.
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Arylpiperazines, such as 1-(3-trifluoromethylphenyl)piperazine (TFMPP) and its chloro analogue mCPP, are 5-HT$_1$ agonists, whereas quipazine, i.e., 2-(1-piperazino)quinoline, appears to be a 5-HT$_2$ agonist. Radioligand binding studies using rat cortical membrane homogenates and drug discrimination studies using rats trained to discriminate a 5-HT$_1$ agonist (i.e., TFMPP) or a 5-HT$_2$ agonist (i.e., 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM)) from saline reveal that quipazine and its 1-deaza analogue 2-naphthylpiperazine (2-NP) bind at 5-HT$_1$ and 5-HT$_2$ sites but produce stimulus effects similar to those of DOM. A structurally related compound, 1-naphthylpiperazine (1-NP), possesses a high affinity for 5-HT$_1$ (K_i = 5 nM) and 5-HT$_2$ (K_i = 18 nM) sites. 1-NP produces stimulus effects similar to those of TFMPP and is able to antagonize the stimulus effects produced by DOM. The present results suggest that the unsubstituted benzene ring of quipazine, and of its 1-deaza analogue 2-naphthylpiperazine, makes a significant contribution to the binding of these agents to 5-HT$_2$ sites and, more importantly, may account for their 5-HT$_2$ agonist properties.

Central serotonin (5-HT) binding sites have been divided into two major populations: 5-HT$_1$ sites, which display a high affinity for tritiated 5-HT, and 5-HT$_2$ sites, which display a high affinity for tritiated spiperone and ketanserin.[1,2] Arylpiperazines constitute a group of fairly se-

† Virginia Commonwealth University.
‡ Albany Medical College.

(1) Peroutka, S. J.; Snyder, S. H. *Mol. Pharmacol.* 1979, *16*, 687.

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Table I. 5-HT_1 and 5-HT_2 Binding Data[a]

	5-HT_1		5-HT_2	
agent	K_i, nM	slope	K_i, nM	slope
quipazine (**2a**)	230 (±22)	0.62 (±0.05)	230 (±8)	0.74 (±0.03)
2b	415 (±70)	0.50 (±0.04)	310 (±20)	0.64 (±0.03)
2c	1 900 (±370)	0.65 (±0.02)	1 200 (±40)	0.90 (±0.09)
6a	>100 000		>150 000	
6b	33 000		71 000	
7a	25 000		50 000	
7b	45 000		50 000	
8a	28 600		79 000	
8b	10 400 (±1850)		35 000	
2-aminotetralin (**9**)	380 (+30)	0.76 (±0.03)	11 100 (±890)	
3-aminoquinoline (**10**)	56 000		>300 000	
11	135 (±10)	0.62 (±0.06)	2 100 (±150)	0.93 (±0.03)
2-NP (**12**)	265 (±80)	0.49 (±0.01)	70 (±8)	0.99 (±0.01)
1-NP (**13**)	5 (±1)	0.74 (±0.08)	18 (±2)	0.70 (±0.02)

[a] K_i values and slopes are followed by SEM in parentheses. SEMs are not presented for those agents with a K_i of >15,000 nM, and slopes were not determined for agents with K_i values of >10,000 nM.

lective 5-HT_1 agonists;[3-5] examples of these types of agents are 1-(3-trifluoromethylphenyl)piperazine (TFMPP; **1a**) and its chloro counterpart mCPP (**1b**). TFMPP serves as a training drug in tests of stimulus control of behavior in rats; furthermore, the TMFPP stimulus generalizes to mCPP suggesting that both agents produce similar behavioral (i.e., stimulus) effects in animals.[6] Quipazine (**2a**) is another example of an arylpiperazine with activity as a 5-HT agonist. However, quipazine (a) does not display selectivity for 5-HT_1 binding sites, (b) does not produce behavioral effects similar to those produced by TFMPP, mCPP, and other phenylpiperazines (PPIPs), and (c) produces effects that appear to be 5-HT_2-mediated.[4,5] For example, TFMPP stimulus generalization does not occur with quipazine,[7] in contrast, using animals trained to discriminate agents that reportedly produce their stimulus effects via a 5-HT_2 mechanism, e.g., 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM; **3**, R = CH_3), generalization occurs with quipazine but not with TFMPP or mCPP.[4,8] Quipazine itself has been used as a training drug in drug discrimination studies;[9,10] the available evidence suggests that the quipazine stimulus is 5-HT_2-mediated.[8-10] Although quipazine was first reported nearly 20 years ago,[11] very little is known regarding its structure–activity relationships (SAR). The present study was not intended to be a comprehensive SAR investigation; however, we were interested in attempting to determine why quipazine behaves differently from other arylpiperazines.

(2) Leysen, J. E.; Niemegeers, C. J. E.; Van Nueten, J. M.; Laduron, P. M. *Mol. Pharmacol.* **1982**, *21*, 301.
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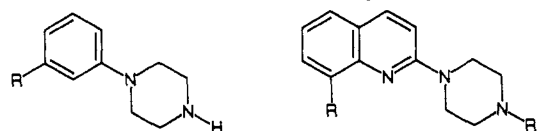
(9) Friedman, R. L.; Barrett, R. J.; Sanders-Bush, E. J. *Pharmacol. Exp. Ther.* **1984**, *228*, 628.
(10) For an overview of quipazine as a discriminative stimulus, see: Glennon, R. A.; Rosecrans, J. A.; Young, R. In *Drug Discrimination: Applications in CNS Pharmacology*; Colpaert, F. C., Slangen, J. L., Eds.; Elsevier Biomedical: Amsterdam, 1982; p 69.
(11) Hong, E.; Sancillio, L. F.; Vargas, R. *Eur. J. Pharmacol.* **1969**, *6*, 274.

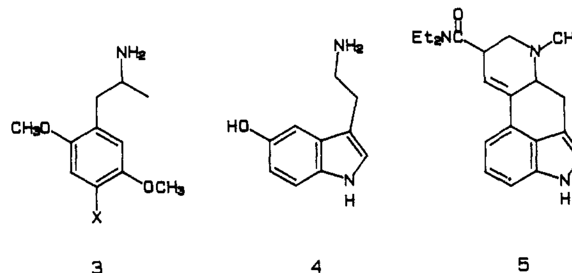
Serotonin (**4**) possesses a high affinity for 5-HT binding sites;[1,12] LSD (**5**) also interacts with high affinity, but with



1a R = CF_3 2a R = H, R' = H

1b R = Cl 2b R = OMe, R' = H

2c R = OMe, R' = Me

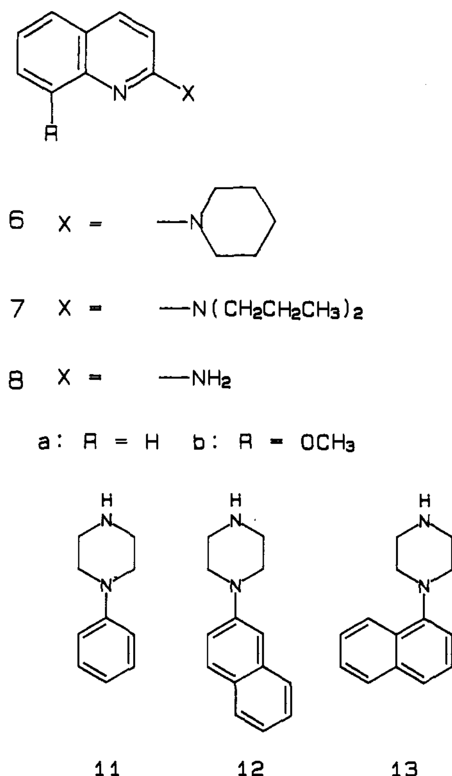


little selectivity, at 5-HT_1 and 5-HT_2 sites[1] suggesting that these binding sites may share a similar aromatic ring/terminal amine orientation. With this in mind, a study was undertaken to determine how quipazine might interact with these sites.

Chemistry. Synthesis of the quipazine analogues **2b**, **2c**, and **6–8** was straightforward and involved, for the most part, displacement of the chloro group of 2-chloroquinoline or 2-chloro-8-methoxyquinoline (**14**) with the appropriately substituted amine. The naphthylpiperazines **12** and **13** were prepared by the reaction of bis(2-chloroethyl)amine with the appropriate naphthylamine.

Binding Studies. Binding studies were conducted using rat cortical membrane homogenates; [^{3}H]-5-HT and [^{3}H]ketanserin were used to label 5-HT_1 and 5-HT_2 sites, respectively. The results of competition studies are shown in Table I. Quipazine (**2a**) possesses an equivalent affinity (K_i = 230 nM) for both types of 5-HT binding sites. In general, replacement of the piperazine group of quipazine (**2a**) with a piperidino, di-*n*-propylamino, or amino group (i.e., **6a–8a**, respectively) resulted in a greatly diminished affinity for 5-HT_1 and 5-HT_2 sites. Introduction of the 8-methoxy group (i.e., **2b**, **6b–8b**) had essentially no effect on affinity. In the one case examined, N-monomethylation

(12) Titeler, M.; Herrick, K.; Lyon, R. A.; McKenney, J. D.; Glennon, R. A. *Eur. J. Pharmacol.* **1985**, *117*, 145.



of the piperazine ring (i.e., **2c**) resulted in a 5–10-fold decrease in affinity. The monocyclic piperazine derivative 1-phenylpiperazine (**11**) was slightly more potent than quipazine at 5-HT_1 sites (K_i = 135 nM) but was 10 times less potent than quipazine at 5-HT_2 sites (K_i = 2100 nM). Benz-fusion at the c-face of **11** to afford 2-NP (**12**) resulted in a 5-HT_2-selective (K_i = 70 nM) agent, whereas benz-fusion at the b-face to afford 1-NP (**13**) resulted in a dramatic increase in affinity both at 5-HT_1 (K_i = 5 nM) and 5-HT_2 (K_i = 18 nM) sites.

Discrimination Studies. Tests of stimulus generalization were conducted with 1-NP (**13**) and 2-NP (**12**) using rats trained to discriminate either TFMPP or DOM from saline, and with phenylpiperazine (**11**) in the DOM-trained animals. The TFMPP stimulus generalized to 1-NP but not to 2-NP (Table II). The DOM stimulus generalized to 2-NP but not to 1-NP or phenylpiperazine (Table II). In tests of stimulus antagonism, 1-NP (at 1.0 mg/kg) was able to shift the dose–response curve of DOM to the right (Figure 1) suggesting that 1-NP can act as an antagonist of the DOM stimulus.

Discussion

Initially, in order to determine the importance of the 4-position nitrogen, several simple analogues of quipazine were examined. These included **6a** (where the 4-position piperazine nitrogen is replaced by carbon), **7a** (a 2-dialkylamino quinoline derivative), and **8a** (2-aminoquinoline itself). The role of the aromatic nitrogen was examined by evaluation of compound **12** (2-naphthylpiperazine (2-NP) or 1-deazaquipazine). There is a possibility that quipazine interacts with 5-HT binding sites in such a manner that the 8-position of the quinoline ring might correspond to the 5-position of serotonin (i.e., in a fashion resembling the 2-aminotetralin portion of LSD). Although this type of interaction is remote, because of the reduced basicity of the 2-amino group of quinoline relative to that of 2-aminotetralin (**9**), Kotler-Brajtburg[13] has reported that 3-aminoquinoline is a potent serotonin antagonist and,

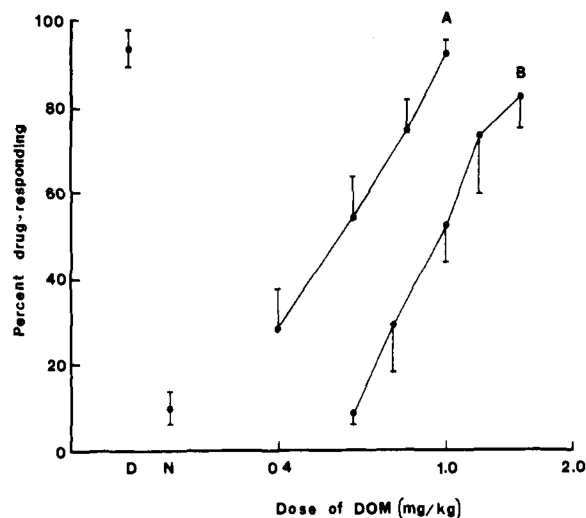


Figure 1. Dose–response curve for the effect of DOM HCl in DOM-trained rats in the absence (A) and in the presence (B) of 1.0 mg/kg of 1-NP (**13**). Percent drug-appropriate responding is the number of responses made on the DOM-designated lever as a percent of total responses made during a 2.5-min extinction session and reflects the responding of 4–8 animals at each data point; D, effect of 1.0 mg/kg of DOM HCl preceded (by 15 min) by an injection of 1.0 mL/kg of 0.9% saline; N, effect of 1.0 mg/kg of 1-NP followed (by 15 min) by an injection of 1.0 mL/kg of 0.9% saline (n = 6 in each case).

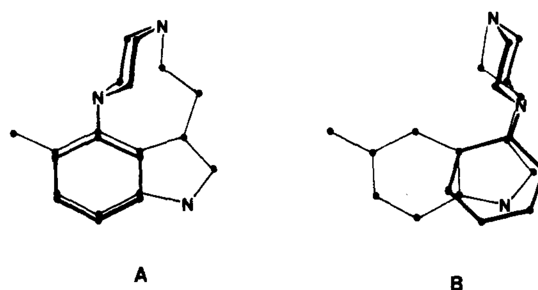


Figure 2. Two representations for the possible overlap of the structures of a phenylpiperazine (heavy lines) and serotonin at serotonin binding sites. The aromatic portion of the phenylpiperazine may be congruent with the benzene ring (A) or the pyrrole portion (B) of serotonin.

further, that reduction of the pyrido ring results in a decrease in potency. Thus, in order to rule out this possibility, several 8-methoxy analogues of the above compounds, that is **2b**, **2c**, and **6b**–**8b**, were examined; 2-aminotetralin (**9**) and 3-aminoquinoline (**10**) were also included in the evaluation for comparative purposes. Comparing the affinity of quipazine with those of **6a**–**8a**, it is clear that the 4-position piperazine nitrogen is necessary for binding both at 5-HT_1 and 5-HT_2 sites. Introduction of the methoxy group (i.e., **2b**, **6b**–**8b**) has little effect on either 5-HT_1 or 5-HT_2 binding, and 2-aminotetralin (**9**) is significantly more potent than 2-aminoquinoline (**8a**). 3-Aminoquinoline (**10**) was inactive both at 5-HT_1 and 5-HT_2 sites.

TFMPP (**1a**) and mCPP (**1b**), agents that share a common 1-phenylpiperazine backbone, display selectivity for 5-HT_1 binding sites.[3,14] 1-Phenylpiperazine (**11**) possesses an affinity for 5-HT_1 sites comparable to that of quipazine (Table I); however, unlike quipazine, **11** displays a 15-fold selectivity for 5-HT_1 vs. 5-HT_2 sites. The affinity of 2-NP (**12**), a benz-fused analogue of **11**, for 5-HT_1 sites is similar

(13) Kotler-Brajtburg, J. *Acta Pol. Pharm.* **1966**, *23*, 98.

(14) Lyon, R. A.; Titeler, M.; McKenney, J. D.; Glennon, R. A. *J. Med. Chem.*, in press.

Table II. Results of Stimulus Generalization Studies with 1-NP, 2-NP, and 1-Phenylpiperazine

agent	dose, mg/kg	N^a	% drug-appropriate responding[b] (SEM)	mean resp/min[b] (SEM)	ED_{50},[c] mg/kg
		a. TFMPP-Trained Animals			
1-NP	0.5	3/3	15 (8)	19.1 (4.9)	
	1.0	3/4	41 (12)	17.3 (3.2)	
	2.5	5/5	96 (3)	16.4 (1.1)	1.0 (0.4–2.6)
2-NP	1.0	3/3	6 (3)	20.6 (9.7)	
	3.0	2/3	12 (2)	7.0 (0.6)	
	3.5	2/3	25 (12)	7.0 (1.0)	
	4.0	0/3	*d*		
TFMPP	0.5	6/6	92 (3)	18.2 (2.2)	
saline (1.0 mL/kg)		6/6	12 (4)	17.6 (2.3)	
		b. DOM-Trained Animals			
1-NP	0.5	3/3	14 (3)	18.0 (0.8)	
	2.0	3/4	7 (3)	8.8 (3.4)	
	2.2	2/5	*d*		
	2.5	3/6	37 (15)	2.6 (0.6)	
	2.7	1/4	*d*		
	3.0	1/4	*d*		
2-NP	0.6[e]	3/3	3 (2)	16.1 (7.9)	
	2.5	4/4	33 (14)	16.8 (6.5)	
	3.5	4/4	71 (11)	8.0 (3.2)	
	5.0	3/4	88 (7)	8.7 (1.9)	2.9 (1.9–4.5)
phenylpiperazine (11)	0.05	3/3	7 (3)	13.1 (4.7)	
	0.1	3/3	8 (5)	11.9 (5.0)	
	0.3	0/3	*d*		
	0.5	0/3	*d*		
	2.0	1/4	*d*		
DOM	1.0	10/10	97 (2)	16.3 (3.1)	
saline (1.0 mL/kg)		10/10	14 (6)	16.9 (2.9)	

[a] N = number of animals responding/number to receive dose of drug. [b] Data collected during 2.5-min extinction session. [c] ED_{50} followed by 95% confidence limits. [d] Disruption of behavior (i.e., no responding). [e] The results for the 0.6 mg/kg dose were not used in calculating the ED_{50} value.

to that of quipazine (**2a**) and 2-aminotetralin (**9**). However, whereas its affinity at 5-HT_2 sites is only 3 times that of quipazine, it is greater than 150 times that of 2-aminotetralin. 1-Phenylpiperazine (**11**) and 2-NP (**12**) display similar affinities for 5-HT_1 sites, but the affinity of **11** for 5-HT_2 sites is 5 times that of 2-aminotetralin and $^1/_{30}$ that of 2-NP. These findings suggest that the unsubstituted aromatic ring of 2-NP (and of quipazine) is making a significant contribution to the 5-HT_2 site interaction.

There are several different orientations that can be envisioned for the interaction of arylpiperazines with 5-HT binding sites (Figure 2). One possibility is that in which the six-member aromatic rings and terminal amines of 5-HT and the arylpiperazines are overlayed; we have previously made such a suggestion.[14] Another possibility is that the aromatic portion of the arylpiperazines occupies a site on the receptor with which the pyrrole portion of 5-HT normally interacts. The results of the present study are insufficient to allow us to distinguish between these two types of interactions. Nevertheless, if the aromatic portion of the arylpiperazines occupies only one part of the aromatic binding site (e.g., the benzene portion but not the pyrrole portion), it may be possible to enhance the affinity (though not necessarily the selectivity) of 1-phenylpiperazine (**11**) by benz-fusion at the b-face to afford 1-napthylpiperazine (1-NP; **13**). Indeed, the affinity of 1-NP is 25 times that of **11** at 5-HT_1 sites and greater than 100 times that of **11** at 5-HT_2 sites (Table I). Consequently, if the pyrido ring of quipazine (or the corresponding ring of 2-NP) occupies one of these two sites (or one site for 5-HT_1 binding and the other site for 5-HT_2 binding), the unsubstituted ring is situated in the region associated with the 7-7a-1 position of 5-HT. This is consistent with the results obtained with phenylisopropylamine analogues.[15] That is, the structure of LSD (**5**) contains a phenylisopropylamine (as well as a 2-aminotetralin) unit; most phenylisopropylamines,[15] e.g., 1-(2,5-dimethoxyphenyl)-2-aminopropane (**3**, X = H), like 2-aminotetralin (Table I) lack selectivity for 5-HT_2 sites. However, introduction of hydrophobic substituents (small alkyl groups, halogen) at the phenylisopropylamine 4-position (e.g., **3**, X = CH_3, Br) results in an increase in affinity and selectivity for 5-HT_2 sites.[15]

In drug discrimination studies employing animals trained to discriminate DOM from saline, the DOM stimulus generalizes to quipazine but not to TFMPP.[8] In the present study, the DOM stimulus generalizes to 2-NP but not to 1-NP. Conversely, using animals trained to discriminate the phenylpiperazine TFMPP from saline, stimulus generalization occurs with 1-NP but not with 2-NP (Table II). These results are in accord with the selectivity of these agents for 5-HT binding sites (Table I) (i.e., 2-NP is somewhat selective for 5-HT_2 sites, whereas 1-NP displays some selectivity for 5-HT_1 sites). However, the results are rather disturbing in that (a) the selectivity of these agents for a particular binding site is small and (b) these agents (1-NP in particular) display significant affinity for both types of binding sites. One possible explanation for this is that these agents may differ in their pharmacokinetic (i.e., metabolism, distribution) properties. Another explanation is that they may behave as agonists at one site and as antagonists at the other site. Indeed, while this work was in progress, Cohen et al.[16,17] reported

(15) Shannon, M.; Battaglia, G.; Glennon, R. A.; Titeler, M. *Eur. J. Pharmacol.* **1984**, *102*, 23.
(16) Cohen, M. L.; Fuller, R. W.; Kurz, K. D. *Hypertension* **1983**, *5*, 676.

that 1-NP acts as a serotonin antagonist in peripheral receptor preparations. The TFMPP-trained animals were administered doses of 2-NP prior to administration of TFMPP in an attempt to antagonize the stimulus effects produced by the training drug. Low doses of 2-NP had no effect, and higher doses resulted in disruption of behavior (data not shown); thus, the results of these studies were inconclusive. Similar studies were conducted using DOM-trained animals. Figure 1 shows that pretreatment of the animals with 1.0 mg/kg of 1-NP effectively shifts the dose-response curve of DOM to the right. This suggests that although 1-NP is a 5-HT_1 agonist, it is also a 5-HT_2 antagonist. Thus, it appears that the unsubstituted fused rings of 2-NP and of quipazine may not only contribute to selectivity but (particularly in light of the lack of DOM stimulus generalization to **11**) may also account for the 5-HT_2 agonist effects produced by these agents.

Summary

Various arylpiperazines possess activity as serotonin agonists. Unlike TFMPP (**1a**), which is a 5-HT_1 agonist, quipazine (**2a**) appears to be a 5-HT_2 agonist. The 4-position piperazine nitrogen atom of quipazine is necessary for affinity at 5-HT_1 and 5-HT_2 binding sites, but it does not seem that either this nitrogen or the quinoline nitrogen contributes significantly to selectivity. The results of the present study suggest that the unsubstituted benzene ring of quipazine, and of its 1-deaza counterpart 2-NP (**12**), may contribute to 5-HT_2 binding and may be responsible for the 5-HT_2 agonist effects produced by these agents. 1-NP (**13**), an agent with high affinity for 5-HT_1 and 5-HT_2 sites, produces stimulus effects similar to those of TFMPP (**1a**) and can antagonize the stimulus effects of the 5-HT_2 agonist DOM.

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 were consistent with assigned structures. Melting points were determined by use of a Fisher-Johns melting point apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlab (Atlanta, GA), and determined values are within 0.4% of theoretical. 2-(*N*,*N*-Di-*n*-propylamino)quinoline (**7a**) was prepared according to a literature[18] procedure.

8-Methoxy-2-(piperazin-1-yl)quinoline Maleate (2b). A stirred solution of 2-chloro-8-methoxyquinoline (14) (400 mg, 2 mmol) and 1-piperazinylcarboxaldehyde (5 mL, 48.5 mmol) was heated at reflux for 20 h. The solution was cooled to room temperature and diluted with Et_2O (30 mL). The Et_2O solution was extracted with 10% HCl (2 × 20 mL), and the combined aqueous portions were made basic (10% NaOH, pH >10) and extracted with ether (3 × 25 mL). The combined organic extracts were dried (Na_2SO_4, $MgSO_4$) and evaporated in vacuo to yield an amber oil. The oil was distilled (Kugelrhor, air bath 95–108 °C/0.3 mmHg) to afford 99 mg (20%) of the title compound as a yellow gum. The water-insoluble oxalate salt was prepared: mp 228–231 °C. The maleate salt was prepared: mp 178–179.5 °C after recrystallization from absolute EtOH. Anal. ($C_{14}H_{17}N_3O \cdot C_4H_4O_4$) C, H, N.

2-(4-Methylpiperazin-1-yl)-8-methoxyquinoline Maleate (2c). A stirred solution of 2-chloro-8-methoxyquinoline (14) (1.0 g, 5.16 mmol) and *N*-methylpiperazine (10 mL) was heated at reflux for 4 h. The orange-red solution was diluted with 20% w/v aqueous Na_2CO_3 (25 mL) and extracted with Et_2O (3 × 30 mL). The combined organic portions were dried ($MgSO_4$) and evaporated in vacuo to provide an orange-red liquid. The liquid was distilled (Kugelrhor, air bath 79–90 °C/0.175 mmHg) to afford 735 mg (55%) of the title compound as an amber oil. The maleate salt was prepared: mp 181–183 °C after two recrystallizations from absolute EtOH. Anal. ($C_{15}H_{19}N_3O \cdot C_4H_4O_4$) C, H, N.

2-Piperidinoquinoline Hydrochloride (6a). Compound **6a**, as the free base (mp 48–49 °C), was prepared according to the method of Luthy et al.[18] An ether solution of this amine was treated with HCl gas to afford **6a** as fine white needles: mp 191–193 °C after recrystallization from absolute EtOH. Anal. ($C_{14}H_{16}N_2 \cdot HCl$) C, H, N.

8-Methoxy-2-(piperidin-1-yl)quinoline Hydrochloride (6b). A stirred solution of 2-chloro-8-methoxyquinoline (14) (1.0 g, 5.3 mmol) and piperidine (10 mL) was heated at reflux for 15 h followed by stirring at room temperature for 5 h. The reaction mixture was diluted with H_2O (25 mL) and 20% w/v Na_2CO_3 (25 mL). The aqueous solution was extracted with Et_2O (3 × 50 mL), dried ($MgSO_4$), and evaporated in vacuo to yield a dark oil. The oil was distilled (Kugelrhor, air bath 81–90 °C/0.2 mmHg) to afford the title compound as a viscous amber oil. The oil was dissolved in anhydrous Et_2O, and an anhydrous ethereal-HCl solution was added to precipitate 530 mg (36%) of the hydrochloride salt as white prismatic rods: mp 188–191 °C. Anal. ($C_{15}H_{18}N_2O \cdot 2HCl \cdot H_2O$) C, H, N.

2-(*N*,*N*-Di-*n*-propylamino)-8-methoxyquinoline Hydrochloride (7b). A stirred solution of 2-chloro-8-methoxyquinoline (14) (775 mg, 4 mmol) and *N*,*N*-di-*n*-propylamine (10 mL) was heated at reflux for 80 h. The cooled solution was poured into 20% w/v aqueous Na_2CO_3 (50 mL) and extracted with ether (3 × 50 mL). The combined organic layers were dried (Na_2SO_4, $MgSO_4$) and evaporated in vacuo to yield a yellow-orange oil. The oil was distilled (Kugelrhor, air bath 72–78 °C/0.2 mmHg) to afford the crude product as an amber oil. The product was purified by column chromatography (EtOAc; 5.5-g silica gel; column size, 22 × 1 cm) to yield 114 mg (11%) of the title compound as the first eluent. The HCl salt was prepared: mp 146–148 °C. Anal. ($C_{16}H_{22}N_2O \cdot 2HCl \cdot 2H_2O$) C, H, N.

2-Amino-8-methoxyquinoline (8b). *p*-Toluenesulfonyl chloride (260 mg, 1.4 mmol) was added to a stirred solution of 8-methoxyquinoline *N*-oxide[19] (20 mg, 1.15 mmol) in $CHCl_3$ (8 mL) at room temperature; this was immediately followed by the addition of concentrated NH_4OH (2 mL). The mixture was stirred at room temperature for 2 h followed by dilution with H_2O (5 mL). The organic layer was washed with 10% aqueous HCl (2 × 20 mL), and the aqueous portion was separated and made basic (pH >9) by the addition of concentrated NH_4OH, followed by extraction with Et_2O (2 × 25 mL). The organic portion was dried (Na_2SO_4) and evaporated to dryness to yield a white solid. The solid was recrystallized from H_2O as clear colorless needles (170 mg, 70%): mp 160–162 °C [lit.[20] mp 156 °C].

1-(2-Naphthyl)piperazine Hydrochloride (12). Compound **12** was prepared in the same manner (and on the same scale) as **13** to yield 17.8 g (76%) of the free base as a pale-yellow oil: bp 138–142 °C/0.25 mmHg [lit.[21] bp 130–135 °C/0.25 mmHg]. The mono HBr salt was prepared for purposes of characterization, mp 278–280 °C after recrystallization from absolute EtOH [lit.[22] mp 280 °C), but the HCl salt (mp 265–266 °C after recrystallization from absolute EtOH) was used in the binding and drug discrimination studies.

1-(1-Naphthyl)piperazine Hydrochloride (13). A mixture of 1-aminonaphthalene hydrochloride (20 g, 111 mmol), bis(2-chloroethyl)amine hydrochloride (23.3 g, 131 mmol), K_2CO_3 (36.2 g, 262 mmol), and diglyme (75 mL) was heated at reflux for 48 h. The cooled reaction mixture was poured into H_2O (200 mL), and the solution was made basic to ca. pH 12 by the addition of a saturated aqueous solution of KOH and was extracted with EtOAc (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent was removed under reduced pressure

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to afford approximately 20 g of a dark oil. Vacuum distillation gave 16.1 g (68%) of **13** as the free base: bp 148–156 °C/0.1 mmHg [lit.[21] bp 144–147 °C/1 mmHg]. A small sample of the amine was converted to the HBr salt: mp 293–295 °C after recrystallization from absolute EtOH [lit.[22] unmelted at 290 °C]. A saturated solution of HCl gas in anhydrous Et_2O was added to 10 g of the amine in 50:50 mixture of Et_2O–absolute EtOH to yield 8.8 g of the title product after recrystallization from absolute EtOH: mp 313–315 °C. Anal. ($C_{14}H_{16}N_2$·HCl) C, H, N.

2-Chloro-8-methoxyquinoline (14). Method A. Phosphorous oxychloride (0.16 mL, 1.67 mmol) was added all at once to 8-methoxyquinol-2-one[19] (250 mg, 1.4 mmol), and the stirred mixture was heated at 85–90 °C (H_2O bath) for 20 min. The orange solution was poured onto crushed ice (ca. 10 g) in 100 mL of H_2O. The aqueous solution was extracted with Et_2O (2 × 100 mL); the aqueous portion was neutralized with solid Na_2CO_3 followed by extraction with Et_2O (1 × 100 mL). The combined Et_2O extracts were dried (Na_2CO_3) and evaporated to dryness in vacuo to afford 253 mg (93%) of a yellow viscous oil, which solidified upon standing: mp 85–87 °C [lit.[23] mp 82 °C].

Method B. Phosphorous oxychloride (3.2 mL, 34.5 mmol) was added dropwise to a stirred solution of 2-ethoxy-8-methoxyquinoline[19] (3.0 g, 15.7 mmol) in dry DMF (20 mL) at 0 °C. After complete addition, the reaction mixture was heated at 75–85 °C (oil bath) for 2 h. The mixture was cooled to 0 °C, quenched with a saturated solution of aqueous NaOAc (10 mL), and then warmed on a H_2O bath for 30 min. The solution was allowed to cool to room temperature and was extracted with Et_2O (3 × 50 mL). The Et_2O extracts were washed with H_2O (3 × 75 mL), dried (Na_2SO_4), and evaporated to dryness in vacuo to yield a light-brown oil. Purification by flash chromatography (EtOAc; rate, 2 in./min) afforded 2.8 g (92%) of a viscous yellow oil, which solidified upon standing: mp 84–87 °C.

Binding Studies. The radioligand binding assay was conducted in essentially the same manner as reported earlier.[15] Frontal cortex was prepared from male Taconic Farms Sprague-Dawley rats (ca. 200 g) and was either frozen (−80 °C) for later use or was 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 $MgCl_2$, 0.5 mM Na_2EDTA, 0.1% ascorbic acid, and 10 μM pargyline according to the method of Leysen et al.[2] The assays were performed in triplicate in 2.0 mL of buffer to which membranes (3 mg wet weight for 5-HT_2 binding, or 8 mg wet weight for 5-HT_1 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) and [^{3}H]serotonin (21.6 Ci/mmol) were used to label 5-HT_2 and 5-HT_1 sites, respectively. Nonspecific binding was measured by using 1 μM cinanserin (5-HT_2) or 1 μM serotonin (5-HT_1). 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 using NEN 963 in a Beckman 3801 scintillation counter at an efficiency of 50%. Competition data were analyzed by use of a computer-assisted nonlinear least-squares regression analysis to obtain IC_{50} values and pseudo-Hill coefficients.[24] 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. The present study employed two groups of male Sprague-Dawley rats that had been previously trained to discriminate either 1.0 mg/kg of DOM HCl ($n = 10$) or 0.5 mg/kg of TFMPP HCl ($n = 6$) from saline,[14,25] using a standard two-lever operant procedure and a variable-interval (15 s) schedule of reinforcement for food reward. See Glennon and Hauck[25] for a more detailed description of the training and testing procedures used herein. In brief, maintenance of the original DOM/saline and TFMPP/saline discriminations were ensured by continuation of training sessions throughout the present studies. During the stimlus generalization 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. 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 drug-appropriate (i.e., DOM- or TFMPP-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, ED_{50} 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. In the stimulus antagonism studies, doses of 1-NP (or 2-NP) were administered 15 min prior to the administration of doses of DOM (or TFMPP); 15 min later, discrimination responding was evaluated during a 2.5-min extinction session.

Note Added in Proof. Using the new radioligand [^{3}H]DOB[12] to label 5-HT_2 sites, we have now shown that quipazine (**2a**) displays a 10-fold higher affinity (K_i = 17 nM) than it does for [^{3}H]ketanserin-labeled 5-HT_2 sites (unpublished findings).

Registry No. **2b**, 104090-80-4; **2b** (free base), 104090-79-1; **2b** (free base) (oxalate), 104090-91-7; **2c**, 104090-82-6; **2c** (free base), 104090-81-5; **6a**, 104090-83-7; **6a** (free base), 46708-03-6; **6b**, 104090-84-8; **6b** (free base), 104090-89-3; **7a**, 104090-88-2; **7b**, 104090-85-9; **7b** (free base), 104090-90-6; **8a**, 580-22-3; **8b**, 104090-86-0; **9**, 2954-50-9; **10**, 580-17-6; **11**, 92-54-6; **12**, 104090-87-1; **12** (free base), 57536-91-1; **13**, 104113-71-5; **13** (free base), 57536-86-4; **14**, 74668-74-9; 1-piperazinylcarboxaldehyde, 7755-92-2; *N*-methylpiperazine, 109-01-3; piperidine, 110-89-4; *N*,*N*-di-*n*-propylamine, 142-84-7; 8-methoxyquinoline *N*-oxide, 22614-90-0; 1-aminonaphthalene hydrochloride, 552-46-5; bis(2-chloroethyl)amine hydrochloride, 821-48-7; 8-methoxyquinol-2-one, 59-31-4; 2-ethoxy-8-methoxyquinoline, 46185-83-5.

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