In a similar manner, ***cis*-(−)-(6a*R*,13b*R*)-11-chloro-6,6a,7,8,9,13b-hexahydro-7-methyl-5*H*-benzo[*d*]naphth[2,1-*b*]azepin-12-ol [(−)-2a]**, $[\alpha]^{26}_D$ −31.3° (*c* 1.016, DMF), was obtained starting from (−)-17.

Acknowledgment. We acknowledge Dr. S. Airy of the Physical Analytical Chemistry Department of Schering-Plough for developing the chiral HPLC assay, Drs. L. C. Iorio and R. D. McQuade of the Department of Pharmacology, Schering-Plough, for determining the in vitro binding constants, Dr. E. H. Gold for helpful discussions, and Messrs. W. F. Kluttz and B. Vibulbhan for expert technical assistance.

Supplementary Material Available: Listings of bond lengths, bond angles, torsional angles, hydrogen and non-hydrogen atomic coordinates, isotropic thermal parameters, and anisotropic temperature factor parameters for **1c**, (−)-**2a**, (−)-**2b**, **4**, **7**, and **12**, solid-state conformations of **4**, **7**, and **12**, and coordinates in SYBYL file format for modeled conformations of **1c**, **2a**, and **2b** (76 pages). Ordering information is given on any current masthead page.

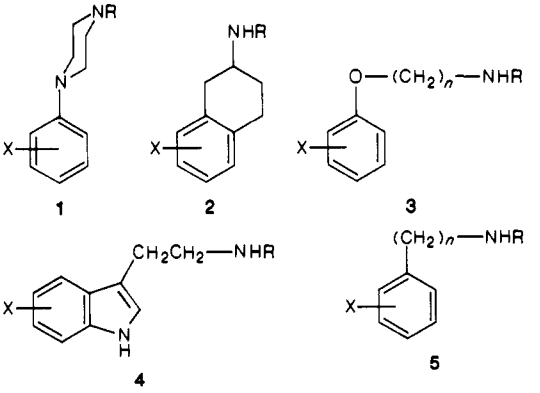
N-(Phthalimidoalkyl) Derivatives of Serotonergic Agents: A Common Interaction at 5-HT_{1A} Serotonin Binding Sites?

Richard A. Glennon,*[†] Noreen A. Naiman,[†] M. Edward Pierson,[†] J. Doyle Smith,[†] Abd M. Ismaiel,[†] Milt Titeler,[‡] and Robert A. Lyon[‡,§]

Department of Medicinal Chemistry, School of Pharmacy, Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia 23298-0581, and Department of Pharmacology, Albany Medical College, Albany, New York 12208.
Received January 9, 1989

Several classes of agents are known to bind at central 5-HT_{1A} serotonin sites. In order to challenge the hypothesis that these agents bind in a relatively similar manner (i.e., share common aryl and terminal amine sites), we prepared *N*-(phthalimidobutyl) derivatives of examples of several such agents. With regard to arylpiperazines, we had previously shown that introduction of this functionality at the terminal amine is tolerated by the receptor and normally results in a significant (>10-fold) enhancement in affinity. The results of the present study show that this bulky functionality is also tolerated by the receptor when incorporated into examples of all other major classes of 5-HT_{1A} agents (e.g., 2-aminotetralin, phenylalkylamine, indolylalkylamine, and (aryloxy)alkylamine derivatives). The length of the alkyl chain that separates the terminal amine from the phthalimido group is of major importance, and a four-carbon chain appears optimal. Alteration of the length of this chain can have a significant influence on affinity; decreasing the chain length from four to three carbon atoms can reduce affinity by an order of magnitude, and further shortening can have an even more pronounced effect.

Of the different populations of central serotonin (5-HT) receptors, 5-HT_{1A} sites have probably received the most attention. We, and others, have previously demonstrated that several classes of agents bind at these sites (for example, see ref 1–3 for recent reviews). Prominent among such agents are certain (a) arylpiperazines **1**, (b) 2-aminotetralins **2**, (c) (1-aryloxy)alkylamines **3**, and (d) indolylalkylamines **4**; phenylalkylamines **5** also bind at these sites although they do so with somewhat lower affinity. Although the affinity (and, indeed, selectivity) of these agents can be modulated by the presence and location of certain substituent groups, casual inspection of these structures reveals that all possess an aromatic moiety and a terminal amine group. It would not be difficult to envision each of these agents interacting at 5-HT_{1A} receptors in such a manner so as to share common aryl and terminal amine binding sites. Indeed, the results of recent molecular modeling studies strongly support the likelihood of such an interaction;[4] on the basis of these studies, binding models have been proposed. In these models, a mean distance between the center of a common aromatic nucleus and the terminal amine was found to be between 5.0 and 5.6 Å.[4] Several years ago, we conducted some preliminary modeling studies demonstrating that arylpiperazines, indolylalkylamines, and phenylalkylamines could share common aromatic to terminal amine distances, suggesting that members of each of these classes might interact at 5-HT receptors in a similar manner.[5] We subsequently undertook a synthetic investigation, the purpose of which was to gain some empirical support for this hypothesis.

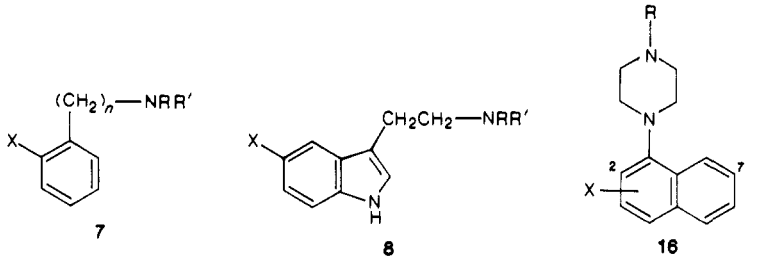


[†] Virginia Commonwealth University.
[‡] Albany Medical College.
[§] Present address: Miami Valley Laboratories, Procter and Gamble Co., P.O. Box 398707, Cincinnati, OH 45239-8707.

(1) Glennon, R. A. *J. Med. Chem.* **1987**, *30*, 1.
(2) Fozard, J. *Trends Pharmacol. Sci.* **1987**, *8*, 501.
(3) Glennon, R. A. In *Receptor Pharmacology and Function*; Williams, M., Glennon, R. A., Timmermans, P. B. M. W. M., Eds.; Marcel Dekker: New York, 1989; p 257.
(4) (a) Hibert, M. F.; Gittos, M. W.; Middlemiss, D. N.; Mir, A. K.; Fozard, J. R. *J. Med. Chem.* **1988**, *31*, 1087. (b) Hibert, M.; Middlemiss, D. N.; Fozard, J. R. In *Brain 5-HT1A Receptors*; Dourish, C. T., Ahlenius, S., Hutson, P. H., Eds.; Ellis Horwood: Chichester, 1987; p 27. (c) Smith, D. W.; Yocca, F. D.; Hyslop, D. K.; Eison, M. S.; Taylor, D. P. *Soc. Neurosci. Abstr.* **1986**, *12*, 422.
(5) Lyon, R. A.; Titeler, M.; McKenney, J. D.; Magee, P. S.; Glennon, R. A. *J. Med. Chem* **1986**, *29*, 680, and unpublished findings.

0022-2623/89/1832-1921$01.50/0

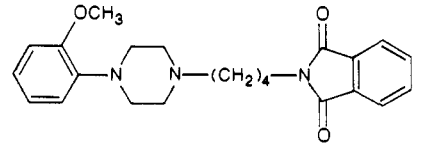
Table I. 5-HT_{1A} Binding Data for Several *N*-Butylphthalimides and Related Compounds



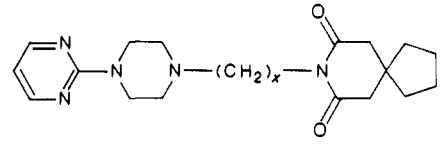
	n	X	R′	R	K_i, nM[a]	Hill slope[a]
7a	2	H	H	NBP[b]	240 (±25)	0.89 (±0.08)
7b	2	H	Me	NBP	300 (±20)	1.06 (±0.06)
7c	2	H	Me	Me	850 (±60)	0.99 (±0.05)
7d	3	H	H	NBP	65 (±3)	1.00 (±0.02)
7e	3	OMe	H	NBP	110 (±15)	0.99 (±0.05)
7f	3	OMe	Me	NBP	170 (±5)	1.02 (±0.02)
7g[c]	3	OMe	Me	Me	3200 (±300)	0.90 (±0.06)
8a		OMe	H	NBP	20 (±4)	1.02 (±0.08)
8b		OMe	Me	Me	10 (±2)	0.91 (±0.02)
16a		2-OMe		H	34 (±1)	0.88 (±0.01)
16b[d]		7-OMe		H	3.3 (±0.8)	1.20 (±0.20)

[a] K_i and Hill slope values are followed by SEM in parenthesis. [b] NBP = *N*-(4-phthalimidobutyl). [c] Synthesis previously reported.[18] [d] For purpose of comparison, the K_i value for 5-methoxytryptamine = 3.2 nM.[19]

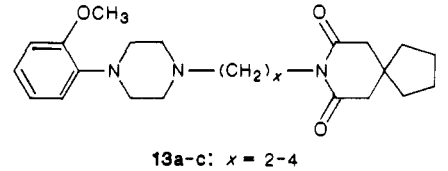
We have previously examined a series of arylpiperazine derivatives **1** and have demonstrated that introduction of an *N*-(phthalimidobutyl) (NBP) group at the terminal amine not only is tolerated but can result in significantly enhanced (>10-fold) affinities at 5-HT_{1A} sites relative to those derivatives where R = H.[6] Indeed, the arylpiperazine **6a** (NAN-190) represents one of the highest affinity 5-HT_{1A} agents (K_i = 0.6 nM) reported to date.[6,7] Our working hypothesis, then, is that if **1–5** bind at a common terminal amine site, the bulky *N*-(phthalimidobutyl) group should be tolerated in each case. Ideally, introduction of this functionality should also enhance affinity to the same extent in each case. As a consequence, we prepared and evaluated examples of several such derivatives.



6a



12a-c: x = 2-4



13a-c: x = 2-4

Chemistry

For the most part, the phthalimido compounds were prepared by simply allowing the appropriate *N*-(bromoalkyl)phthalimide to react with the requisite amine. Compound **7e** was additionally prepared by the reaction of 1,4-diaminobutane with 2-methoxycinnamaldehyde, followed by catalytic reduction of the imine and reaction of the terminal amine with phthalic anhydride. Eschweiler–Clarke methylation of **7e** afforded **7f**. 5-Methoxytryptamine was reductively alkylated with 4-(2-phthalimido)butyraldehyde and sodium cyanoborohydride to give the indole derivative **8a**. Piperazine derivatives **16a** and **16b** were prepared by reaction of the appropriate methoxynaphthylamine with bis(2-chloroethyl)amine.

Results and Discussion

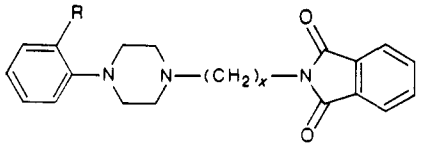
The first group of compounds examined were the phenylalkylamines **5** where n = 2 and 3 (i.e., **7a–g**). Replacement of the *N*-methyl group of **7c**, where n = 2, with the NBP group (i.e., **7b**) has little effect on affinity (K_i = 850 and 300 nM, respectively) (Table I). Where n = 3, replacement of the *N*-methyl group of **7g** with the NBP group (i.e., **7f**) is also tolerated, and results in about a 20-fold increase in affinity (Table I). The presence or absence of the R′ methyl group seems to have little effect on affinity (compare **7a** with **7b**, or **7e** with **7f**). The affinity of the NBP analogue of 5-methoxy-*N*,*N*-dimethyltryptamine (**8b**), i.e., **8a**, is similar to that of **8b** (K_i: **8a** = 20 nM; **8b** = 10 nM; Table I). Although there was no significant enhancement in affinity, it is evident in this latter case that the NBP group is tolerated in that **8a** still binds with high affinity at 5-HT_{1A} sites.

We had previously noted that the distance between the aryl portion and the phthalimido group might be important for affinity.[6] There is additional support for this argument when the affinities of **7b** and **7f** are compared with those of their *N*,*N*-dimethyl counterparts **7c** and **7g**, respectively (see Table I). Furthermore, if the affinities of *N*-(ethyl-, *N*-(propyl-, *N*-(butyl-, and *N*-(pentylphthalimido)phenylpiperazine derivatives **9a–d** are compared (see Table II), it is apparent that the length of the alkyl chain plays a pivotal role and that a chain length, x, of 4 or 5 is optimal.[6]

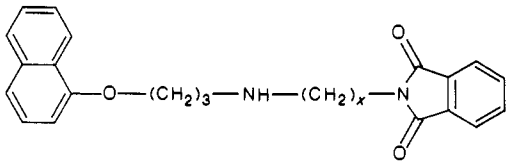
We next examined the NBP derivative of the (1-aryloxy)alkylamines **3** (i.e., **10c**). Again, the NBP group is tolerated and the affinity of **10c** is 15 times that of its *N*,*N*-dimethyl counterpart [i.e., *N*,*N*-dimethyl-3-(1-

(6) Glennon, R. A.; Naiman, N. A.; Lyon, R. A.; Titeler, M. *J. Med. Chem.* **1988**, *31*, 1968.
(7) Glennon, R. A.; Naiman, N. A.; Pierson, M. E.; Titeler, M.; Lyon, R. A.; Weisberg, E. *Eur. J. Pharmacol.* **1988**, *154*, 339.

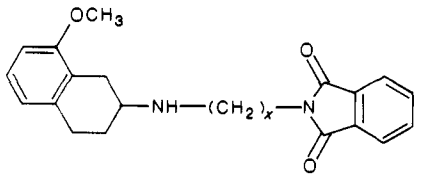
Table II. 5-HT_{1A} Binding Data for *N*-Alkylphthalimides



6: R = OCH_3
9: R = H



10



11

	x	K_i, nM[a]	Hill slope[a]
6a[b]	4	0.6	
6b	5	5.0 (±0.8)	0.90 (±0.11)
9a[b]	2	>10 000	
9b[b]	3	200	
9c[b]	4	10	
9d[b]	5	8.5	
10a	2	1 330 (±270)	0.87 (±0.02)
10b	3	45 (±7)	1.20 (±0.10)
10c	4	25 (±8)	1.11 (±0.07)
11a	2	250 (±25)	1.31 (±0.07)
11b	3	48 (±6)	0.96 (±0.03)
11c	4	11 (±1)	0.78 (±0.03)

[a] K_i value and Hill slope followed by SEM in parenthesis. [b] Data previously reported;[6] included for comparative purposes.

naphthyloxy)propanamine hydrochloride; K_i = 345 nM].[8] With this series, we also examined the effect of shortening the length of the alkyl group that separates the terminal amine from the phthalimido nitrogen atom. As with the arylpiperazines, when x = 2 the compound possesses a low affinity for 5-HT_{1A} sites (**10a**; K_i = 1330 nM). However, unlike the arylpiperazines, when x = 3 the affinity of the resultant compound is similar to that of **10c** (i.e., **10b**; K_i = 45 nM). Apparently, shorter chain lengths may have different effects on affinity, depending upon the aromatic portion of the molecule.

In the final series of compounds to be examined (i.e., derivatives of **2**), we again varied the chain length x from two to four carbon atoms. As anticipated, the affinity of the aminotetralin derivative **11a** where x = 2 displays the lowest affinity. The three-carbon chain analogue **11b** (K_i = 48 nM) possesses a somewhat higher affinity, and its four-carbon analogue **11c** (K_i = 11 nM) possesses the highest affinity within the series. [Although we have not prepared the corresponding *N,N*-dimethyl analogue of 8-methoxy-2-aminotetralin for purposes of comparison, we have previously reported the affinity of 8-methoxy-2-aminotetralin itself (**2**, R = H, X = 8-OCH_3; K_i = 53 nM).[9]]

Admittedly, some of these differences in affinity are small; however, there is a consistent trend among the

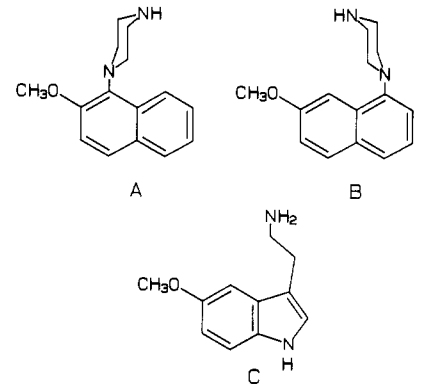


Figure 1. Structural relationship between 1-(2-methoxy-1-naphthyl)piperazine (A) (**16a**), 1-(7-methoxy-2-naphthyl)-piperazine (B) (**16b**), and 5-methoxytryptamine (C).

different series. In each case, the NBP group is tolerated, and in each case (with the exception of the indolylalkylamines), the affinity of the NBP derivative is greater than that of the corresponding primary or *N,N*-dimethylamine derivative. Where the length of the alkyl chain between the terminal amine and the phthalimido group was varied, a four-carbon chain was found to be optimal. These results suggest that all three groups of agents (i.e., **9–11**) might utilize a common site to accommodate the phthalimido portion of the molecule and that the length of the side chain plays a role in determining affinity. Because the indolylalkylamine derivative **8a** did not show a significant affinity enhancement over that of **8b**, it might be speculated that different chain lengths are required to accommodate subtle (or, perhaps, not so subtle) differences in the binding of the aryl portions of agents **1–5**. For example, removal of the 5-methoxy group of 5-methoxytryptamine (**4**, R = H, X = 5-OCH_3), the 5-hydroxy group of 5-HT (**4**, R = H, X = 5-OH), the 8-methoxy group of 8-methoxytetralin derivatives (**2**, X = 8-OCH_3), or the 2-methoxy group of (2-methoxyphenyl)piperazine derivatives (**1**, X = 2-OCH_3) all result in a 10-fold decrease in affinity.[1,8,9] Yet removal of the 2-methoxy group of **7e** (i.e., **7d**) has little effect on affinity. This would argue against a common binding orientation for the aryl portions of these arylalkylamines. Similarly, removal of the 2-methoxy group of *N,N*-dimethyl-3-(2-methoxyphenoxy)propanamine, or the 2-hydroxy group of *N,N*-dimethyl-3-(2-hydroxyphenoxy)propanamine, has no effect on 5-HT_{1A} affinity.[8] Furthermore, upon varying the length of the side chain for a series of 1-(2-pyrimidinyl)piperazine azaspirodecanedione imides **12a–c**, Yocca and co-workers reported results that parallel ours in that the affinity of the four-carbon chain analogue (**12c**; buspirone) is greater than that of its two- or three-carbon chain counterparts (i.e., IC_{50} values at 5-HT_{1A} sites are 150, 200, and 30 nM for **12a–c**, respectively).[10] However, using a different arylpiperazine moiety, the affinity of the four-carbon chain analogue **13c** (IC_{50} = 2 nM) is nearly identical with that of the two-carbon chain analogue **13a** (BMY-7378; IC_{50} = 2.4 nM); both possesses a higher affinity than the three-carbon chain analogue **13b** (IC_{50} = 80 nM).[10,11]

Naphthyl derivatives, such as **15**, offer a special problem. Molecular modeling studies by Hibert and co-workers[4a,b] have raised the possibility that the naphthyl portion of **15** might be accommodated by 5-HT_{1A} sites in more than one

(8) Pierson, M. E.; Lyon, R. A.; Titeler, M.; Kowalski, P.; Glennon, R. A. *J. Med. Chem.*, **1989**, *32*, 859.
(9) Naiman, N. A.; Lyon, R. A.; Bullock, A. E.; Rydelek, L. T.; Titeler, M.; Glennon, R. A. *J. Med. Chem.* **1989**, *32*, 253.
(10) Yocca, F. D.; Smith, D. W.; Hyslop, D. K.; Maayani, S. *Soc. Neurosci. Abstr.* **1986**, *12*, 422.
(11) Yocca, F. D.; Hyslop, D. K.; Smith, D. W.; Maayani, S. *Eur. J. Pharmacol.* **1987**, *137*, 293.

orientation. We have encountered similar problems with the naphthyl derivative of **9c**, i.e., 4-(1-naphthyl)-1-[4-(2-phthalimido)butyl]piperazine (**14**). 1-(1-Naphthyl)-piperazine (**15**) possesses a high affinity for 5-HT_{1A} sites (K_i = 11 nM);[6] consistent with the results of the present study, incorporation of the NBP group results in a 10-fold increase in affinity (**14**; K_i = 1 nM).[6] If it is assumed that the naphthyl nucleus binds at 5-HT_{1A} sites in a manner common to that of 5-HT itself, theoretically either one of the phenyl rings of the naphthyl group might be accommodated by the phenyl portion (i.e., the benzene ring portion of the indolic) 5-HT_{1A} site. (See Figure 1; see also ref 5.) To determine which ring mimics the benzene portion of the indole nucleus, we prepared and evaluated the 2-methoxy and 7-methoxy derivatives of **15** (i.e. **16a** and **16b**, respectively). A 10-fold increase in affinity over that of **15** was expected from that agent which placed the methoxy group in a region comparable to the methoxy group of 5-methoxytryptamine. Unfortunately, the results were somewhat ambiguous; the affinity of **16a** (K_i = 34 nM) (Table I) was one-third that of **15** (K_i = 11 nM), whereas the affinity of **16b** (K_i = 3.3 nM) was only 3 times that of **15**. Thus, although the affinity of **16b** is nearly identical with that of 5-methoxytryptamine itself (K_i = 3.2 nM), this question must remain unanswered for the time being.

The most important finding of the present study is that the large NBP group is tolerated by members of every major class of agents known to display significant affinity for 5-HT_{1A} sites. In general, introduction of this functionality also seems to enhance affinity (the one exception being that of the indolylalkylamine derivative). Chain length is a critical factor in determining optimal affinity, and one methylene group can have a significant influence (for example, compare the affinities of **9a** and **9b**); this may explain the results obtained with the more conformationally flexible indolylalkylamine **8a**. Nevertheless, many of the derivatives reported herein possess very high affinities for 5-HT_{1A} sites. At this time, the nature of the interaction of the phthalimido portion of these agents with the receptor is only speculative, but it may involve a hydrophobic interaction. For example, removal of the phthalimido group (i.e., deprotection) of **9c** (K_i = 10 nM), to afford the primary amine (K_i > 6000 nM), results in a dramatic decrease in affinity.[6] Furthermore, for a series of N4-substituted arylpiperazines, Abou-Gharbia and co-workers have noted that affinity for 5-HT_{1A} sites increases with increasing lipophilicity of the N4-substituent.[12]

In summary, then, the results of the present study are in complete agreement with molecular modeling studies and lend some support to the hypothesis that agents **1–5** bind at 5-HT_{1A} sites in a similar manner. That is, these agents probably utilize a common aryl, terminal amine and phthalimido site; however, the exact orientation of the aryl portions of these agents is in need of further study.

Experimental Section

Synthesis. Proton magnetic resonance spectra were obtained on a JEOL FX90 spectrometer with tetramethylsilane as internal standard. Infrared spectra were recorded on a Nicolet 5ZDX FT-IR. Spectral data are consistent with the assigned structures. Melting points were determined by using a Thomas-Hoover melting point apparatus and are uncorrected. Microanalysis was performed by Atlantic Microlab, and determined values are within 0.4% of theory.

1-(2-Methoxyphenyl)-4-[5-(2-phthalimido)pentyl]-piperazine Hydrochloride (6b). The title compound was prepared in 39% yield from *N*-(5-bromopentyl)phthalimide and 1-(2-methoxyphenyl)piperazine according to the same procedure employed for the synthesis of **7a**. Recrystallization was from 2-propanol, mp 133–134 °C. Anal. ($C_{24}H_{29}N_3O_3$·HCl·0.25H_2O) C, H, N.

***N*-[4-(2-Phthalimido)butyl]-2-phenyl-1-aminoethane Hydrochloride (7a).** *N*-(4-Bromobutyl)phthalimide (1.16 g, 4.13 mmol) in MeCN (10 mL) was added in a dropwise manner to a stirred mixture of 2-phenyl-1-aminoethane (0.5 g, 4.13 mmol) and K_2CO_3 (1.14 g, 8.25 mmol) in MeCN (20 mL). The mixture was heated at reflux for 4 h, and the solid material was removed from the hot solution by filtration. As the filtrate cooled, an off-white product precipitated from solution. Recrystallization from MeCN afforded 300 mg (23%) of the free base of **7a**, mp 227.5–229 °C. A dry ethereal solution of HCl was added to a portion of the free base in Et_2O to yield the HCl salt, mp 227–229 °C. Anal. ($C_{20}H_{22}N_2O_2$·HCl·0.5H_2O) C, H, N.

***N*-Methyl-*N*-[4-(2-phthalimido)butyl]-2-phenyl-1-aminoethane Hydrochloride (7b).** Compound **7b** was prepared as described for **7a** by using *N*-methyl-2-phenyl-1-aminoethane (0.5 g, 3.7 mmol). The free base was isolated as an oil. A solution of the oil in 10% HCl was extracted with Et_2O (3 × 10 mL); the aqueous portion was basified by the addition of 15% NaOH solution and extracted with Et_2O (3 × 15 mL). The Et_2O fractions were dried (Na_2SO_4), and the solvent was removed under reduced pressure to yield a yellow oil. The oil was chromatographed on silica (10 g, column diameter 13 mm); the appropriate fractions were combined and evaporated to yield an oily product. The HCl salt was prepared as shown to yield 250 mg (19%) of **7b** after recrystallization from 2-propanol/Et_2O, mp 144–148 °C. Anal. ($C_{21}H_{24}N_2O_2$·HCl) C, H, N.

***N*-[4-(2-Phthalimido)butyl]-3-phenyl-1-aminopropane Hydrochloride (7d).** The title compound was prepared in 26% yield in a manner similar to that used for the synthesis of **7a**, with recrystallization from absolute EtOH/Et_2O, mp 146–147.5 °C. Anal. ($C_{21}H_{24}N_2O_2$·HCl) C, H, N.

***N*-[4-(2-Phthalimido)butyl]-3-(2-methoxyphenyl)-1-aminopropane Hydrochloride (7e). Method A.** Glacial HOAc (0.56 g, 9.3 mmol) and 1,4-diaminobutane (0.82 g, 9.3 mmol) were added to a solution of 2-methoxycinnamaldehyde (0.5 g, 3.1 mmol) in absolute EtOH (10 mL) to which 4-Å molecular sieves had been added. The solution was allowed to stir at room temperature under a nitrogen atmosphere for 2.5 h. The sieves were removed by filtration, and the filtrate was diluted by the addition of absolute EtOH (50 mL) and hydrogenated at 45 psi for 70 min in the presence of PtO_2 (25 mg). The catalyst was removed by filtration, and the filtrate was evaporated under reduced pressure. A solution of the oily residue in 10% aqueous HCl (10 mL) was extracted with Et_2O (3 × 5 mL); the aqueous portion was basified by the addition of 15% NaOH (10 mL) and extracted with $CHCl_3$ (3 × 8 mL). The combined $CHCl_3$ portions were dried ($MgSO_4$), and the solvent was removed under reduced pressure to afford a yellow oil. The oil was chromatographed on silica gel (10 g, 13-mm diameter column) by elution with EtOAc/EtOH/NH_4OH (10:10:1). The appropriate fractions were combined and evaporated to dryness to yield 350 mg (48%) of *N*-[3-(2-methoxyphenyl)propyl]-1,4-diaminobutane. A suspension of this material (1.08 g, 4.6 mmol), NEt_3 (0.52 g, 5.1 mmol), and phthalic anhydride (0.74 g, 5.0 mmol) in toluene (25 mL) was heated under reflux with continuous removal of H_2O by using a Dean–Stark trap. The mixture was allowed to cool to room temperature, and the toluene solution was washed with 15% NaOH (2 × 20 mL) and H_2O (2 × 20 mL) and dried. The solvent was removed under reduced pressure to afford a yellow oil which was subsequently purified by chromatography on silica gel (10 g, 13-mm diameter column) with EtOAc as eluent. The first 50 mL was discarded; the second 50 mL was evaporated to dryness to yield 500 mg (30%) of the title compound as the free base. The product was identical with the free base prepared by method B.

Method B. *N*-(4-Bromobutyl)phthalimide (110 mg, 0.39 mmol) in MeCN (5 mL) was added to a dropwise manner to a stirred suspension of 3-(2-methoxyphenyl)-1-aminopropane[13] (64 mg, 0.39

(12) Abou-Gharbia, M.; Patel, U. R.; Webb, M. B.; Moyer, J. A.; Andree, T. H.; Muth, E. A. *J. Med. Chem.* **1988**, *31*, 1382.

(13) Morishita, H.; Nakano, S.; Satoda, I.; Omoto, T. Japanese Patent 3365, 1959; *Chem. Abstr.* **1959**, *53*, 18912.

mmol) and K_2CO_3 (110 mg) in MeCN (10 mL). The stirred reaction mixture was heated at reflux for 8.5 h and allowed to cool to room temperature, and the inorganic material was removed by filtration. The filtrate was evaporated under reduced pressure; the residue was dissolved in 10% aqueous HCl, washed with Et_2O (3 × 5 mL), basified with 15% NaOH (20 mL), and extracted with $CHCl_3$ (3 × 10 mL). The combined $CHCl_3$ portions were dried ($MgSO_4$), evaporated to dryness, and purified by column chromatography on silica gel (10 g, 13-mm column diameter) by elution with $CHCl_3$/MeOH (9:1). The appropriate fractions were combined and evaporated under reduced pressure to yield 35 mg (25%) of the title compound as a colorless oil (free base). The hydrochloride salt was prepared as described for **7a**, with recrystallization from MeCN, mp 108–109 °C. Anal. ($C_{22}H_{26}N_2O_3$·HCl) C, H, N.

***N*-Methyl-*N*-[4-(2-phthalimido)butyl]-3-(2-methoxyphenyl)-1-aminopropane Hydrochloride (7f).** Formic acid (97%; 190 mg, 4 mmol) and formaldehyde (37%; 280 mg, 3.5 mmol) was added to the free base of **7e** (490 mg, 1.34 mmol) at 0 °C. The mixture was heated at 75–80 °C (oil bath temperature) for 16 h. The mixture was allowed to cool to room temperature, 5% aqueous HCl (15 mL) was added, and the acidic solution was extracted with Et_2O (3 × 10 mL). The aqueous portion was basified with 15% aqueous NaOH (10 mL) and extracted with Et_2O (3 × 12 mL), and the combined Et_2O extracts were dried (Na_2SO_4) and evaporated under reduced pressure to yield a dark yellow oil. The oil was chromatographed on silica gel (9 g, column diameter 13 mm) by elution with $CHCl_3$/MeOH (3:1); the first 15 mL were discarded, the next 40 mL were combined, and the solvent was removed under reduced pressure to yield 445 mg (87%) of a pale yellow oil. The hydrochloride salt was prepared and recrystallized from absolute EtOH/Et_2O to give **7f** as white crystals, mp 144–146 °C. Anal. ($C_{23}H_{28}N_2O_3$·HCl).

5-Methoxy-3-[2-[4-(2-phthalimido)butyl]amino]ethyl]-indole Hydrochloride (8a). 4-(2-Phthalimido)butyraldehyde[14] (70 mg, 0.32 mmol) in dry MeOH (1 mL) and $NaCNBH_3$ (12 mg, 0.2 mmol) were added to a solution of 5-methoxytryptamine (300 mg, 1.58 mmol) and 5 N HCl/MeOH (0.14 mL) in MeOH (5 mL) in the presence of 3-Å molecular sieves. The pH was adjusted to 7 by the addition of additional HCl/MeOH solution. The solution was allowed to stir at room temperature for 50 h, the molecular sieves were removed by filtration, and the filtrate was acidified to pH 2 by addition of glacial acetic acid. The solvent was removed under reduced pressure, and a solution of the yellow residue in H_2O (10 mL) was washed with Et_2O (3 × 6 mL), basified with 15% NaOH, and extracted with Et_2O (7 mL) and then $CHCl_3$ (2 × 7 mL). The combined organic fractions were dried ($MgSO_4$), and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (10 g silica gel, 13-mm column diameter) with $CHCl_3$/MeOH (4:1) as eluent. The first 25 mL was discarded, and the next 65 mL were combined and evaporated under reduced pressure to yield the free base as a yellow oil. The hydrochloride salt was prepared and recrystallized from absolute EtOH/Et_2O to yield 30 mg (22%) of **8a** as fine yellow needles, mp 127.5–130 °C. Anal. ($C_{23}H_{25}N_3O_3$·HCl) C, H, N.

***N*-[2-(2-Phthalimido)ethyl]-3-(1-naphthyloxy)propanamine Hydrochloride (10a).** *N*-(2-Bromoethyl)phthalimide (0.34 g, 1.3 mmol) in MeCN (10 mL) was added in a dropwise manner to a stirred suspension of amine **17** (0.2 g, 1 mmol) and K_2CO_3 (0.3 g, 1.3 mmol) in MeCN (30 mL) heated at reflux. Heating at reflux was continued for another 18 h, and the reaction mixture was filtered hot. The filter cake was washed with hot MeCN (2 × 5 mL), and the combined filtrates were evaporated under vacuum to afford an oil. The oil was chromatographed (20 g of silica gel, 28-mm column diameter) with EtOAc as eluent. The appropriate fractions were combined and treated with a dry ethereal solution of HCl to yield the crude product. Recrystallization from absolute EtOH afforded 0.22 g (54%) of the title compound as small yellow needles, mp 203–205 °C. Anal. ($C_{23}H_{22}N_2O_3$·HCl) C, H, N.

***N*-[3-(2-Phthalimido)propyl]-3-(1-naphthyloxy)propanamine Hydrochloride (10b).** Compound **10b** was prepared in 25% yield from amine **17** and *N*-(3-bromopropyl)phthalimide according to the same procedure employed for **10a**. Recrystallization was from a MeOH/toluene mixture, mp 218–221 °C. Anal. ($C_{24}H_{24}N_2O_3$·HCl) C, H, N.

***N*-[4-(2-Phthalimido)butyl]-3-(1-naphthyloxy)propanamine Hydrochloride (10c).** Compound **10c** was prepared in 44% yield from *N*-(4-bromobutyl)phthalimide and amine **17** according to the same procedure used for **10a**. Recrystallization was from 2-PrOH, mp 167–168 °C. Anal. ($C_{25}H_{26}N_2O_3$·HCl) C, H, N.

8-Methoxy-*N*-[2-(2-phthalimido)ethyl]-2-aminotetralin Hydrochloride (11a). The title compound was prepared in 47% yield from 8-methoxy-2-aminotetralin and *N*-(2-bromoethyl)-phthalimide according to the same procedure described for the synthesis of **7e** (method B). Recrystallization was from absolute EtOH/Et_2O, mp 240–242 °C. Anal. ($C_{21}H_{22}N_2O_3$·HCl) C, H, N.

8-Methoxy-*N*-[3-(2-phthalimido)propyl]-2-aminotetralin Hydrochloride (11b). The title compound was prepared in 33% yield from 8-methoxy-2-aminotetralin and *N*-(3-bromopropyl)-phthalimide according to the procedure described for **7e** (method B). Recrystallization was from absolute EtOH/Et_2O, mp 235–237 °C. Anal. ($C_{22}H_{24}N_2O_3$·HCl) C, H, N.

8-Methoxy-*N*-[4-(2-phthalimido)butyl]-2-aminotetralin Hydrochloride (11c). Compound **11c** was prepared from 8-methoxy-2-aminotetralin in 40% yield according to the same procedure used for the preparation of **7b** (method B), with recrystallization from absolute EtOH/Et_2O, mp 235–239 °C. Anal. ($C_{23}H_{26}N_2O_3$·HCl) C, H, N.

1-(2-Methoxy-1-naphthyl)piperazine Hydrochloride (16a). A solution of 1-nitro-2-methoxynaphthalene (1.0 g, 4.9 mmol) in EtOAc (60 mL) was subjected to catalytic hydrogenation in a Parr hydrogenator (60 psi H_2) with 10% Pd/C (0.1 g) as the catalyst. After the reduction, the catalyst was removed by filtration and the solvent was removed in vacuo to yield an oil. The oil was distilled (Kugelrohr, 105–120 °C, 0.11 mm Hg).

Freshly distilled 2-methoxynaphthylamine (7.0 g, 40 mmol), K_2CO_3 (5.5 g, 40 mmol), and bis(2-chloroethyl)amine hydrochloride (7.1 g, 40 mmol) in diglyme (40 mL) were heated to 130 °C under a nitrogen atmosphere for 24 h. Additional K_2CO_3 (2.8 g, 20 mmol) and bis(2-chloroethyl)amine hydrochloride (3.5 g 20 mmol) were added, and heating was continued for an additional 24 h. The mixture was allowed to cool to room temperature, and H_2O (25 mL) and then solid KOH (to pH 12) were added. The organic layer was decanted and evaporated in vacuo. The resulting black gum was dissolved in H_2O (350 mL), layered with toluene (200 mL), and the solution acidified to pH 5, with 1 N HCl, and heated to 100 °C. The aqueous layer was collected by pipet and treated with decolorizing charcoal. The H_2O was removed under reduced pressure to leave a black solid that was dissolved in EtOH and EtOAc (1:1) and subjected to column chromatography [gradient EtOAc to EtOAc/EtOH (1:1), 150 g of silica gel, 45-mm column diameter]. The fractions that cochromatographed were combined, and the solvent was removed. The resulting solid was recrystallized from 2-PrOH to yield 2.0 g (20%) of white needles, mp 213.5–215.5 °C. An analytical sample was prepared by recrystallization from MeOH, followed by heating with toluene to remove residual alcohol and drying for 12 h at 110 °C under reduced pressure, mp 214–215 °C. Anal. ($C_{15}H_{18}N_2O$·HCl) C, H, N.

1-(7-Methoxy-1-naphthyl)piperazine Hydrochloride (16b). 8-Amino-2-methoxynaphthalene (18) (1.8 g, 10.1 mmol), bis(2-chloroethyl)amine hydrochloride 2.7 g, 15 mmol), and K_2CO_3 (2.1 g, 15.0 mmol) were heated at reflux in DMF (10 mL) for 48 h. The solvent was removed and H_2O (10 mL) added to the residue. The mixture was layered with toluene and heated to 100 °C. The H_2O was removed and the toluene solution extracted with H_2O (2 × 10 mL). The aqueous fractions were combined and basified (solid KOH to pH 12), and the product was extracted with Et_2O (3 × 40 mL). The combined Et_2O fractions were dried ($MgSO_4$) and evaporated in vacuo to yield a dark oil. The oil was chromatographed (10 g of silica gel, 20-mm column diameter) with $CHCl_3$/MeOH (9:1) as eluent. The fractions that cochromatographed were combined, and the solvent was removed under reduced pressure. An ethereal solution of HCl gas was added dropwise to an ethereal solution of the product until salt formation ceased. The solvent was removed by decantation, and the solid was washed with Et_2O. Recrystallization from 2-PrOH and then

(14) Karpetsky, T. P.; White, E. H. *Tetrahedron* **1973**, *29*, 3761.

MeOH/anhydrous Et_2O yielded 0.4 g (15%) as a white solid, mp 258–259 °C. Anal. ($C_{15}H_{18}N_2O$·HCl) C, H, N.

3-(1-Naphthyloxy)propanamine (17). Sodium methoxide (25% solution in MeOH; 5.2 g, 26 mmol of NaOMe) was added to 1-naphthol (3.5 g, 24 mmol) in dry MeOH (3 mL) and the solution allowed to stir for 15 min. The MeOH was removed under reduced pressure and replaced with DMF (10 mL); a solution of *N*-(3-bromopropyl)phthalimide (5.0 g, 18.5 mmol) in DMF (7 mL) was added, and the mixture was heated under a nitrogen atmosphere for 8 h. The reaction mixture was cooled to −20 °C and diluted with water; the crude product was collected by filtration, washed with water, and recrystallized from MeCN to afford 4.6 g (75%) of the phthalimido derivative, mp 144–145.5 °C. The phthalimide was deprotected by using hydrazine hydrate; hydrazine hydrate (85% aqueous solution, 2.3 g) in 95% EtOH (15 mL) was added in a dropwise manner to a stirred solution of the phthalimide (4.0 g, 12.1 mmol) in EtOH (100 mL), and the solution was heated at reflux for 3 h. At the end of this time, the precipitate was removed by filtration and was washed with hot EtOH (3 × 30 mL). The combined filtrate was evaporated under reduced pressure, and the residue was basified by the addition of 1 N NaOH (30 mL) and extracted with Et_2O (3 × 50 mL). The combined Et_2O fractions were dried ($MgSO_4$), and the solvent was removed under reduced pressure to afford an oily product. The original basic solution was also extracted with CH_2Cl_2 (3 × 50 mL); the combined CH_2Cl_2 portions were dried ($MgSO_4$), and the solvent was removed under reduced pressure to yield an oil. The oils from both extractions were combined and distilled (Kugelrohr, 50–65 °C; 0.09 mm) to yield 2.2 g (90%) of the title compound. A small sample of the product was converted to the benzoate salt for purposes of identification, mp 133–135 °C (lit.[15] mp 136–137 °C).

8-Amino-2-methoxynaphthalene (18). Method A. A solution of 8-acetamido-2-methoxynaphthalene (1.34 g, 6.1 mmol) and concentrated HCl (2 mL) in 95% EtOH (10 mL) was heated at reflux for 2 h. The solvent was removed in vacuo, and a basic solution (1 N NaOH) of the crude product was extracted with Et_2O (3 × 15 mL). The combined organic fractions were dried ($MgSO_4$) and evaporated in vacuo to afford the title compound as a low-melting yellow solid that was used without further purification, mp 70–72 °C (lit.[16] mp 75–77 °C).

Method B. NaOMe in MeOH (25%, 5.4 mL) was added to purified 8-amino-2-naphthol (3.7 g, 23 mmol) in MeOH (15 mL), and the solvent was removed to yield a white solid. Dimethyl sulfate (1.74 g, 13.8 mmol) was added dropwise to an acetone solution of this sodium salt of 8-amino-2-naphthol, and the reaction mixture was allowed to stir at room temperature for 24 h. The solvent was removed in vacuo to yield an oil. A basic solution of the oil in aqueous KOH (pH 12) was extracted with Et_2O (3 × 15 mL). The combined Et_2O fractions were dried ($MgSO_4$) and evaporated in vacuo to yield a yellow solid. The solid was distilled (Kugelrohr, 60–70 °C, 0.065 mmHg) to yield 1.75 g (44%) of product, mp 70–72 °C. The products prepared by methods A and B were identical by thin-layer chromatography.

Binding Studies. The radioligand binding assay was conducted in essentially the same manner as reported earlier.[17] Male Sprague-Dawley rats (ca. 220 g) were decapitated, and the brains were removed, placed in 0.9% ice-cold saline, and dissected over ice until the tissue was prepared. Tissues were stored in ice-cold saline for not longer than 1 h and, following blot drying and weighing, were either used or frozen at −30 °C until needed. Freshly dissected (or frozen) tissue was homogenized in 30 volumes of ice-cold buffer containing 50 mM Tris·HCl (pH 7.4 at 37 °C; pH 8.0 at 4 °C), 0.5 mM Na_2EDTA, and 10 mM $MgSO_4$, and centrifuged at 30000*g* for 15 min. The supernatant was discarded; the pellet was resuspended and preincubated for 15 min at 37 °C. The pellet was washed twice by centrifugation and resuspension. The final assay buffer contained 50 mM Tris·HCl (pH 7.7), 10 μM pargyline, 0.1% ascorbate, 10 mM $MgSO_4$, and 0.5 mM Na_2EDTA. The 5-HT_{1A} receptor was labeled with 0.1 nM [^{3}H]-8-hydroxy-2-(di-*n*-propylamino)tetralin ([^{3}H]OH-DPAT) (157 Ci/mmol; New England Nuclear) and 4 mg wet weight of rat hippocampal tissue. 8-OH-DPAT (1 μM) was used to determine nonspecific binding. Eleven concentrations of nonradioactive competing drugs were made fresh daily in assay buffer. Following incubation with membranes and radioligand at 37 °C for 20 min, samples were rapidly filtered over glass fiber filters (Schleicher & Schuell) and were washed with 10 mL of ice-cold 50 mM Tris·HCl buffer. Individual filters were inserted into vials and equilibrated with 5 mL of scintillation fluid (ScintiVerse, Fisher) for 6 h before counting at 45% efficiency in a Beckman 3801 counter. Results were analyzed by using the program EBDA in order to determine IC_{50}, K_i, and Hill values. See Titeler et al.[17] for greater detail.

Acknowledgment. This work was supported in part by PHS Grant NS23520.

Registry No. 6b, 120991-49-3; **6b** free base, 120991-50-6; **7a**, 120991-51-7; **7a** free base, 120991-52-8; **7b**, 120991-53-9; **7b** free base, 120991-54-0; **7c**, 10275-21-5; **7c** free base, 1126-71-2; **7d**, 120991-55-1; **7d** free base, 120991-56-2; **7e**, 120991-57-3; **7e** free base, 120991-58-4; **7f**, 120991-59-5; **7f** free base, 120991-60-8; **7g**, 100252-02-6; **7g** free base, 77318-18-4; **8a**, 120991-61-9; **8a** free base, 120991-62-0; **8b**, 2427-79-4; **8b** free base, 1019-45-0; **10a**, 120991-63-1; **10a** free base, 120991-64-2; **10b**, 120991-65-3; **10b** free base, 120991-66-4; **10c**, 120991-67-5; **10c** free base, 120991-68-6; **11a**, 120991-69-7; **11a** free base, 120991-70-0; **11b**, 120991-71-1; **11b** free base, 120991-72-2; **11c**, 120991-73-3; **11c** free base, 120991-74-4; **16a**, 120991-75-5; **16a** free base, 120991-76-6; **16b**, 120991-77-7; **16b** free base, 120991-78-8; **17**, 58477-93-3; **17** benzoate salt, 120991-79-9; *N*-(5-bromopentyl)phthalimide, 954-81-4; 1-(2-methoxyphenyl)piperazine, 35386-24-4; *N*-(4-bromobutyl)-phthalimide, 5394-18-3; 2-phenyl-1-aminoethane, 64-04-0; *N*-methyl-2-phenyl-1-aminoethane, 589-08-2; 1-amino-3-phenylpropane, 2038-57-5; 1,4-diaminobutane, 110-60-1; 2-methoxycinnamaldehyde, 1504-74-1; *N*-[3-(2-methoxyphenyl)propyl]-1,4-diaminobutane, 120991-80-2; phthalic anhydride, 85-44-9; 3-(2-methoxyphenyl)-1-aminopropane, 18655-51-1; 4-(2-phthalimido)butyraldehyde, 3598-60-5; 5-methoxytryptamine, 608-07-1; *N*-(2-bromoethyl)phthalimide, 574-98-1; *N*-(3-bromopropyl)-phthalimide, 5460-29-7; *N*-(3-bromopropyl)phthalimide, 5460-29-7; 8-methoxy-2-aminotetralin, 3880-77-1; 1-nitro-2-methoxynaphthalene, 4900-66-7; 2-methoxy-1-naphthylamine, 2246-42-6; bis(2-chloroethyl)amine, 334-22-5; 8-amino-2-methoxynaphthalene, 5302-79-4; 1-naphthol, 90-15-3; *N*-[3-(1-naphthyloxy)propanyl]-phthalimide, 102196-49-6; 8-acetamido-2-methoxynaphthalene, 93189-18-5; 8-amino-2-naphthol, 118-46-7.

(15) Schaeffer, J. C.; Cho, A. K.; Fischer, J. F. *J. Pharm. Sci.* **1976**, *65*, 122.
(16) Bachman, B.; Picha, G. M. *J. Am. Chem. Soc.* **1946**, *68*, 1599.
(17) Titeler, M.; Lyon, R. A.; Davis, K. H.; Glennon, R. A. *Biochem. Pharmacol.* **1987**, *36*, 3265.
(18) Glennon, R. A.; Salley, J. J.; Steinsland, O.; Nelson, S. *J. Med. Chem.* **1981**, *24*, 678.
(19) Glennon, R. A.; Titeler, M.; Lyon, R. A.; Slusher, M. *J. Med. Chem.* **1988**, *31*, 867.