where $L$ = free ligand concentration and $K_d$ = the dissociation constant for the radioligand determined from saturation studies.

**Acknowledgment.** We wish to acknowledge the excellent technical assistance of Georgina Lambert. This work was supported by NIH Grants NS16605 and NS01009.

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**Registry No.** (+)-**2**, 115649-79-1; (-)-**2**, 115649-80-4; (2*R*)-**3b**, 62501-70-6; (2*S*)-**3b**, 62501-73-9; **4**, 1021-25-6; **5**, 98571-96-1; (2*R*)-**6**, 62501-72-8; (2*S*)-**6**, 98572-00-0; (2*R*,3*R*)-**7**, 98633-62-6; (2*S*,3*S*)-**7**, 98571-97-2; (2*R*,3*R*)-**8**, 115563-58-1; (2*S*,3*S*)-**8**, 115649-81-5; (2*S*,1′*R*)-**9**, 81703-47-1; (2*R*,1′*S*)-**9**, 72522-21-5; (2*S*,1′*R*)-**10**, 115563-59-2; (2*R*,1′*S*)-**10**, 115563-61-6; (2*R*)-**11**, 115563-60-5; (2*S*)-**11**, 115563-62-7; (+)-diethyl tartrate, 87-91-2; (-)-diethyl tartrate, 13811-71-7; *n*-propylamine, 107-10-8; tosyl chloride, 98-59-9.

# Arylpiperazine Derivatives as High-Affinity 5-$HT_{1A}$ Serotonin Ligands

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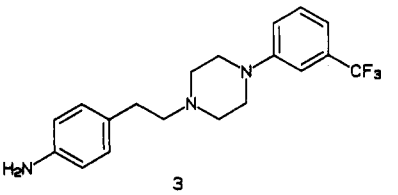
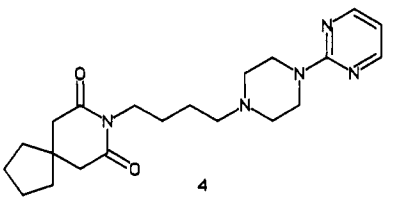
Although simple arylpiperazines are commonly considered to be moderately selective for 5-$HT_{1B}$ serotonin binding sites, N4-substitution of such compounds can enhance their affinity for 5-$HT_{1A}$ sites and/or decrease their affinity for 5-$HT_{1B}$ sites. A small series of 4-substituted 1-arylpiperazines was prepared in an attempt to develop agents with high affinity for 5-$HT_{1A}$ sites. Derivatives where the aryl portion is phenyl, 2-methoxyphenyl, or 1-naphthyl, and the 4-substituent is either a phthalimido or benzamido group at a distance of four methylene units away from the piperazine 4-position, display high affinity for these sites. One of these compounds, 1-(2-methoxyphenyl)-4-[4-(2-phthalimido)butyl]piperazine (**18**), possesses a higher affinity than 5-HT and represents the highest affinity ($K_i$ = 0.6 nM) agent yet reported for 5-$HT_{1A}$ sites.

The discovery of multiple populations of central serotonin (5-hydroxytryptamine; 5-HT) binding sites has rekindled a new interest in this neurotransmitter (see Glennon[1] and Fozard[2] for recent reviews). To date, three populations of sites have been identified (i.e., 5-$HT_1$, 5-$HT_2$, 5-$HT_3$) and there is good evidence of heterogeneity for at least one of these sites (i.e., 5-$HT_{1A}$, 5-$HT_{1B}$, 5-$HT_{1C}$, and 5-$HT_{1D}$ sites).[1,2] Serotonin itself binds at the various 5-$HT_1$ sites with nearly equal affinity;[1] obviously, it is rather important to investigate the structure–activity relationships of agents that bind at these sites (i.e., structure–affinity relationships; SAFIR) so that these results may ultimately lead to the development of high-affinity site-selective agents. Amongst agents that bind at the various 5-$HT_1$ sites, arylpiperazines are the most notable.[1] Two such derivatives that have been extensively investigated are TFMPP (**1**; 1-[3-(trifluoromethyl)phenyl]-piperazine) and its chloro analogue mCPP (**2**); although they possess only a modest selectivity for 5-$HT_{1B}$ sites, they are, nonetheless, considered to be 5-$HT_{1B}$-selective agents (5-$HT_{1B}$ $K_i$ = 30–50 nM).[1,3] At one time it was thought that arylpiperazine moiety might confer selectivity for 5-$HT_{1B}$ sites.[4] However, the discovery of 1-[3(trifluoromethyl)phenyl]-4-[2-(4-aminophenyl)ethyl]piperazine (PAPP, **3**), which binds fairly selectively to 5-$HT_{1A}$ sites,[5] questions this generality. The second-generation anxiolytic (SGA) buspirone (**4**), an arylpiperazine, also binds with high affinity and selectivity at 5-$HT_{1A}$ sites.[6,7] We observed that arylpiperazines (and, indeed, other serotonergic agents) possess a lower affinity for 5-$HT_{1B}$ versus 5-$HT_{1A}$ sites when the terminal amine is a tertiary amine.[1] Recently, we have even demonstrated that conversion of 5-HT to a tertiary amine (i.e., the *N*,*N*-di-*n*-propyl derivative) dramatically reduces its affinity for 5-$HT_{1B}$ sites but has little effect on its affinity at 5-$HT_{1A}$ sites.[8]

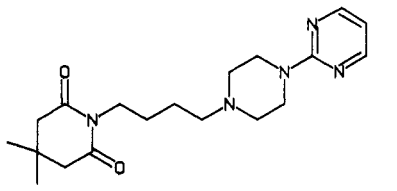
We had earlier concluded that arylpiperazines constitute one of the most versatile structural templates for the investigation of serotonergic agents and that selectivity might



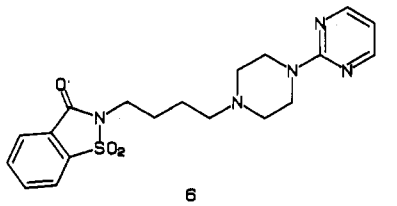

**3**




**4**




**5**




**6**

be achieved by the incorporation of the appropriate substituent groups.[1,9] Knowing now that simple tertiary-

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(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., Eds.; Marcel Dekker: New York, 1988; p 257.
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**Scheme I**

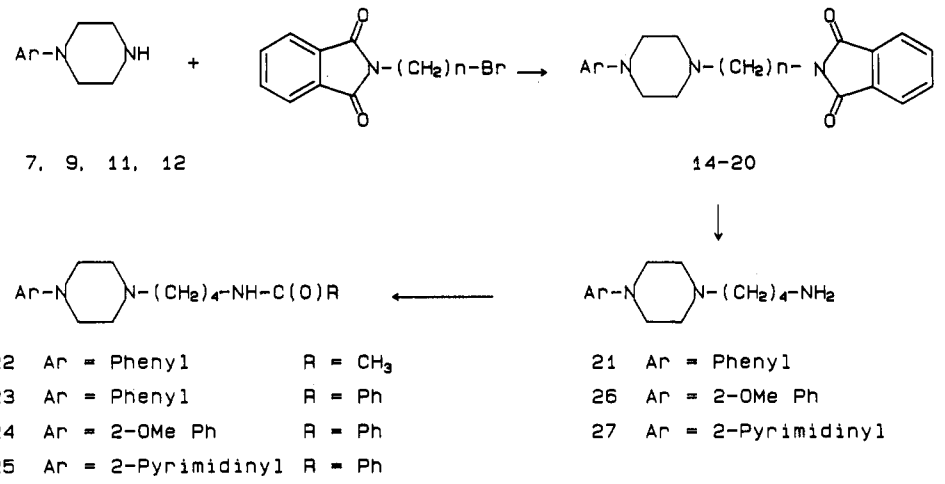


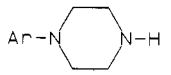

**Table I.** Properties of 4-Substituted Arypiperazines

| no. | method of prep[a] | % yield | mp, °C or (bp, °C/ mmHg) | recrystn solvent | formula[b] |
|---|---|---|---|---|---|
| 14 | A | 44 | 237 dec | abs EtOH | $C_{20}H_{21}N_3O_2$·HCl |
| 15 | A | 42 | 203–206[d] | abs EtOH | |
| 16 | A | 60 | 134–137 | abs EtOH | $C_{22}H_{25}N_3O_2$ |
| 17 | A | 34 | 101–102[e] | *i*-PrOH | |
| 18 | A | 24 | 239–242 | abs EtOH | $C_{23}H_{27}N_3O_3$·HBr[c] |
| 19 | A | 67 | 256–260 | MeOH | $C_{28}H_{27}N_3O_2$·HCl |
| 20 | A | 66 | 138–140[f] | abs EtOH | |
| 21 | B | 26 | 154–156[g] | abs EtOH | $C_{14}H_{23}N_3$·2(COOH)$_2$[c] |
| 22 | C | 19 | 104–106[h] | MeCN | |
| 23 | C | 53 | 142–143 | MeCN | $C_{21}H_{27}N_3O$ |
| 24 | C | 13 | 108–110 | MeCN | $C_{22}H_{29}N_3O_2$ |
| 25 | C | 23 | 106–106.5 | MeCN | $C_{19}H_{25}N_5O$ |
| 26 | B | 67 | (75–80/0.2)[i] | | |
| 27 | B | 48 | (75/0.4)[i] | | |

[a] Method A: Alkylation of arylpiperazine with appropriate *N*-(bromoalkyl)phthalimide (see preparation of **16** in the Experimental Section). Method B: Hydrazinolysis of the appropriate phthalimide (see preparation of **21** in the Experimental Section). Method C: Acylation of the corresponding primary amine. [b] All compounds were analyzed for C, H, N and were within 0.4% of theory. [c] Crystallized with 0.5·$H_2O$. [d] Literature[20] mp 200–202 °C. [e] Literature[21] mp 104–105 °C. [f] Literature[16] mp 137–137.5 °C. [g] Bp (Kugelrohr bath temperature) 71–75 °C (0.3 mm) (lit.[22] bp 147 °C). [h] Literature[23] mp 107–108 °C. [i] Kugelrohr bath temperature; product used without further characterization.

amine analogues of nonselective serotonergic agents possess a lower affinity for 5-HT$_{1B}$ sites than for 5-HT$_{1A}$ sites, our purpose was to prepare arylpiperazine derivatives with high affinity for 5-HT$_{1A}$ sites. The specific goal of the present study was 2-fold: (a) to identify some simple arylpiperazines that bind (though not necessarily selectively) at 5-HT$_{1A}$ sites with an affinity greater than that of TFMPP (**1**) and 1-(2-pyrimidinyl)piperazine (1-PP; **7**) (i.e., the arylpiperazine constituents of PAPP and buspirone), and (b) to structurally modify these arylpiperazines (particularly at the terminal amine) so as to

**Table II.** Affinities of Several Arylpiperazines for [$^3$H]-8-Hydroxy-2-(di-*n*-propylamino)tetralin-Labeled 5-HT$_{1A}$ Sites




| no. | Ar | X | $K_i$,[a] nM | Hill coefficient[a] |
|---|---|---|---|---|
| 1 | 3-$CF_3$-$C_6H_4$ (TFMPP) | N | 175 (±10) | 0.97 (±0.03) |
| 2 | 3-Cl-$C_6H_4$ (mCPP) | N | 130 (±10) | 0.91 (±0.02) |
| 7 | 2-pyrimidinyl (1-PP) | N | 1410 (±60) | 0.95 (±0.04) |
| 8 | $C_6H_5$ | CH | 1520 (±40) | 0.97 (±0.02) |
| 9 | $C_6H_5$ | N | 380 (±25) | 0.95 (±0.02) |
| 10 | 2-OMe-5-Cl-$C_6H_3$ | N | 870 (±50) | 0.97 (±0.02) |
| 11 | 2-OMe-$C_6H_4$ | N | 68 (±7) | 0.88 (±0.01) |
| 12 | 1-naphthyl (1-NP) | N | 11 (±1) | 0.85 (±0.01) |
| 13 | 2-naphthyl (2-NP) | N | 2900 (±470) | 1.02 (±0.09) |

[a] Affinity constants ($K_i$ values) and Hill coefficients are followed by ±SEM.

increase their affinity for 5-HT$_{1A}$ sites. [It should be noted that since our studies were begun, several new SGAs, including gepirone (**5**) and ipsapirone (**6**), have been reported. Although there now exists an extensive literature on the arylpiperazine SGAs (see overviews by Traber and Glaser[10] and by Chopin and Briley,[11] and a review by Young and Glennon),[12] relatively little work has been done on their SAFIR with emphasis on serotonergic binding; this will be discussed further in the Discussison section.]

## Chemistry

The arylpiperazines were alkylated with the appropriate *N*-(bromoalkyl)phthalimide to yield products **14–20** (Table I) as shown in Scheme I. The primary amines **21**, **26**, and **27** were prepared by hydrazinolysis of **16**, **18**, and **20**, respectively. Acylation of **21** with acetic anhydride afforded **22** and with benzoyl chloride afforded **23**. Likewise, **24** and **25** were prepared by acylation of **26** and **27**, respectively, with benzoyl chloride (Table I).

## Results and Discussion

In our initial study, we determined the affinity of a number of arylpiperazine-related derivatives for 5-HT$_{1A}$ binding sites; Table II presents some data for several selected derivatives. It is readily apparent that 1-PP (**7**), the

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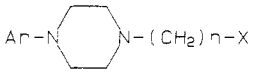
**Table III.** Affinities of 4-Substituted Arylpiperazines for [$^3$H]-8-Hydroxy-2-(di-*n*-propylamino)tetralin-Labeled 5-HT$_{1A}$ Sites




| no. | Ar | n | X | $K_i$, nM (±SEM) | $N$ (±SEM)[a] |
|---|---|---|---|---|---|
| 14 | $C_6H_5$ | 2 | NPhthaloyl | > 10000 | |
| 15 | $C_6H_5$ | 3 | NPhthaloyl | 200 (±10) | 0.99 (±0.01) |
| 16 | $C_6H_5$ | 4 | NPhthaloyl | 10 (±0.5) | 0.99 (±0.01) |
| 17 | $C_6H_5$ | 5 | NPhthaloyl | 8.5 (±0.6) | 0.91 (±0.04) |
| 18 | 2-OMe-$C_6H_4$ | 4 | NPhthaloyl | 0.6 (±0.1) | 0.83 (±0.06) |
| 19 | 1-$C_{10}H_7$[b] | 4 | NPhthaloyl | 1.0 (±0.3) | 1.16 (±0.03) |
| 20 | 2-$C_4H_3N_2$[c] | 4 | NPhthaloyl | 36 (±3) | 1.03 (±0.03) |
| 21 | $C_6H_5$ | 4 | $NH_2$ | > 6000 | |
| 22 | $C_6H_5$ | 4 | $NHCOCH_3$ | 250 (±10) | 0.99 (±0.01) |
| 23 | $C_6H_5$ | 4 | $NHCOC_6H_5$ | 11 (± 2) | 0.82 (±0.03) |
| 24 | 2-OMe-$C_6H_4$ | 4 | $NHCOC_6H_5$ | 2 (±0.1) | 0.88 (±0.06) |
| 25 | 2-$C_4H_3N_2$[b] | 4 | $NHCOC_6H_5$ | 60 (±10) | 0.79 (±0.01) |
| 4 | (buspirone[d]) | | | 15 (± 1) | 0.95 (±0.01) |
| 5 | (gepirone[e]) | | | 70 (± 5) | 1.00 (±0.06) |

[a] Hill coefficient. [b] 1-Naphthyl. [c] 2-Pyrimidinyl. [d] 8-[4-[4-(2-Pyrimidinyl)-1-piperazinyl]butyl]-8-azaspiro[4.5]decane-7,9-dione. [e] 1-[4-[4-(2-Pyrimidinyl)-1-piperazinyl]butyl]piperidine-2,6-dione.

parent arylpiperazine of buspirone, displays a relatively low affinity for these sites. TFMPP (**1**) and mCPP (**2**) display a significantly greater affinity than 1-PP for 5-HT$_{1A}$ sites but are still, nevertheless, selective for 5-HT$_{1B}$ sites by a factor of 3–5-fold.[3] Likewise, 1-naphthylpiperazine (1-NP; **12**), though it possesses a high affinity for 5-HT$_{1A}$ sites, displays an even higher affinity for 5-HT$_{1B}$ sites ($K_i$ = 3 nM; unpublished data). 1-Phenylpiperazine (**9**) and its 2-methoxy derivative, **11**, bind at 5-HT$_{1A}$ sites with an affinity less than that of **12**, but both agents show a several-fold selectivity for 5-HT$_{1A}$ versus 5-HT$_{1B}$ sites (i.e., 5-HT$_{1B}$ $K_i$ = 820 and 120 nM, respectively). Because **9** had a lower affinity than **11** for 5-HT1B sites, it was selected as a template arylpiperazine for further modification.

In the next phase of the study, the piperazine 4-position of **9** was substituted with an alkyl chain; the idea was to vary the length of the alkyl chain, and to incorporate a basic amine at the end of this chain, in an attempt to determine the importance of an amino group (such as that of the less basic amino group found in PAPP). The resulting product, **21**, lacked affinity for either 5-HT$_{1A}$ or 5-HT$_{1B}$ sites ($K_i$ = >6000 nM in both cases). However, the phthaloyl-protected precursor of **21** (i.e., **16**) displayed a high affinity for 5-HT$_{1A}$ sites ($K_i$ = 10 nM; Table III) and a low affinity for 5-HT$_{1B}$ sites ($K_i$ >1000 nM). This was not very surprising given the structural similarity between **16** and buspirone. Shortening the alkyl side chain of **16** by one carbon atom (to afford **15**) reduced 5-HT$_{1A}$ affinity by 20-fold; shortening of the side chain by two carbon atoms resulted in a compound (i.e., **14**) with no affinity for 5-HT$_{1A}$ sites (Table III). Because of the dramatic difference in affinity between **14** and **16**, it would seem that the additional two-carbon chain is not interacting with the receptor in a hydrophobic manner, but is more likely acting as a spacer. On the other hand, increasing the length of the side chain by one methylene group had essentially no effect on affinity (i.e., **17**; Table III). As anticipated, the (2-methoxyphenyl)piperazine and naphthylpiperazine counterparts of **16** (i.e., **18** and **19**) displayed a very high affinity for 5-HT$_{1A}$ sites ($K_i$ values = 0.6 and 1.0 nM, respectively; Table III). Also as anticipated, on the basis of the data in Table II, the affinity of the pyrimidinylpiperazine derivative **20** ($K_i$ = 36 nM) was lower than that of **16**, **18**, and **19**.

In order to determine the necessity of the entire phthalimido group, the structurally simpler acetamido and benzamido derivatives of **16** were evaluated. The affinity of the acetamido analogue, **22**, was 25-fold less than that of **16**, but the benzamido derivative **23** was essentially equipotent with **16** (Table III). The benzamido derivatives **24** and **25** also showed little difference in affinity relative to that of their phthalimido counterparts **18** and **20** (Table III).

Over the past decade or so, there has been considerable interest in the neuroleptic, anxiolytic, antidepressant, and ethopharmacological properties of 4-substituted arylpiperazines.[1-3,10-12] Serotonin has been implicated as playing at least a partial role in the mechanism of action of these agents. One of the more popular agents to be investigated is buspirone; because of its significant affinity for central dopamine binding sites, buspirone was initially developed as a psychosedative/neuroleptic agent;[13-16] however, buspirone, and the structurally related gepirone (which possesses less of a dopaminergic component of action),[16] are now considered to be prototypical nonbenzodiazepine second-generation anxiolytic agents.[10-12] Although there has been a continued interest in developing buspirone-related neuroleptics,[15,16] relatively less effort[17,18] has been made to understand the serotonergic structure–activity aspects of these arylpiperazine derivatives.

The results of the present study reveal the arylpiperazine derivatives with appropriate substituents on the piperazine 4-position nitrogen atom display high affinity for 5-HT$_{1A}$ sites. Use of 4-unsubstituted arylpiperazine components that themselves display a higher affinity than 1-PP (**7**) results in agents with a higher affinity than 1-PP derivatives for 5-HT$_{1A}$ sites. Furthermore, the more complex amide terminus portions of buspirone, gepirone, and related agents do not appear to be necessary for affinity when compared with the structurally simpler benzamido derivatives such as **23** and **24**. Compounds **16–19**, **23**, and **24** possess affinities for 5-HT$_{1A}$ sites that are comparable to, or greater than, that of buspirone (Table III). Indeed, compounds **18**, **19**, and **24** display affinities comparable to that of 5-HT itself (5-HT$_{1A}$ $K_i$ = 2 nM) and represent some of the highest affinity agents yet reported for 5-HT$_{1A}$ sites. The purpose of this present study was to develop agents with high affinity for 5-HT$_{1A}$ sites; however, additional studies are necessary and are currently in progress. Several selected derivatives have been targeted for follow-up study in order to determine their binding profiles and to characterize their pharmacological properties.

## Experimental Section

**Synthesis.** Proton magnetic resonance spectra were obtained with a JEOL FX900 spectrometer with tetramethylsilane as an internal standard; infrared spectra were recorded on a Nicolet 5ZDX FT-IR. Spectral data are consistent with assigned structures. Melting points were determined on a Thomas-Hoover

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capillary melting point apparatus and are uncorrected. Microanalysis was performed by Atlantic Microlab (Atlanta, GA) and determined values are within 0.4% of theory.

**4-Phenyl-1-[4-(2-phthalimido)butyl]piperazine (16).** *N*-(4-Bromobutyl)phthalimide (0.83 g, 2.9 mmol) in xylenes (10 mL) was added dropwise to a warm (oil bath temperature ca. 70 °C) solution of 1-phenylpiperazine (1.0 g, 6.2 mmol) in xylenes (10 mL). After the addition was complete, the reaction mixture was allowed to stir at 120–130 °C for 24 h. The mixture was cooled to 0 °C (ice bath) and the solid material was removed by filtration. Evaporation of the filtrate afforded an orange semisolid material. Recrystallization from absolute EtOH yielded 0.67 g (60%) of **16** as gold needles, mp 134–137 °C.

Compounds **14–18** (Table I) were prepared in the same manner as **16**. Compound **19** and **20** were prepared in like manner except that 2 equiv of $K_2CO_3$ was used in place of excess piperazine and that MeCN was used as solvent in the preparation of **20**. Synthesis of **14–16** and **18–20** employed commercially available *N*-(bromoalkyl)phthalimides; synthesis of **17** required the preparation of *N*-(5-bromo-*n*-pentyl)phthalimide (**28**).[19]

**1-(4-Aminobutyl)-4-phenylpiperazine Dioxalate (21).** A solution of 85% hydrazine hydrate (0.062 g, 1 mmol) in absolute EtOH (1 mL) was added in a dropwise manner to a stirred suspension of compound **16** (0.3 g, 0.83 mmol) in absolute EtOH (5 mL). After the addition was complete, the reaction mixture was heated at reflux for 6 h; additional hydrazine hydrate solution (several drops) was added and heating was continued for 1.25 h. The solution was allowed to cool to room temperature and the solid material was collected by filtration. The filtrate was evaporated under reduced pressure to yield a white solid. The solid material was suspended in 4 N HCl (6 mL) and heated at reflux 3 h. The suspension was chilled to 0 °C and the solid material was removed by filtration. The filtrate was reduced in volume to induce precipitation; the precipitate was removed by filtration and the filtrate was diluted by the addition of water (10 mL) and basified to pH 10 by the addition of 15% NaOH solution. The aqueous solution was extracted with $CHCl_3$ (4 × 15 mL), and the combined organic fractions were dried ($Na_2SO_4$) and evaporated to dryness under reduced pressure. The resulting oil was distilled (Kugelrohr) to afford 0.05 g (26%) of **21** as the free base. The dioxalate salt was prepared by addition of an ethereal solution of the amine to a solution of oxalic acid in $Et_2O$; mp 154–156 °C after recrystallization from absolute EtOH. See Table I.

Amines **26** and **27** (Table I) were prepared in the same manner except that the solids resulting from hydrazinolysis were not heated with HCl. These compounds were distilled (Kugelrohr) and used without further characterization.

**1-Phenyl-4-(*N*-acetyl-4-aminobutyl)piperazine (22).** A solution of **21** (free base: 110 mg, 0.48 mmol) in acetic anhydride (0.5 mL) was allowed to stir under a $N_2$ atmosphere at 0 °C for 30 min and then at room temperature for an additional 30 min (during which time the solution solidified). The product was collected and recrystallized from MeCN to afford 25 mg (19%) of **22** as white crystals, mp 104–106 °C (Table I).

**1-Phenyl-4-(*N*-benzoyl-4-aminobutyl)piperazine (23).** A solution of benzoyl chloride (66 mg, 0.5 mmol) in THF (2 mL) was added in a dropwise manner to a stirred solution of the free base of **21** (110 mg, 0.5 mmol) and triethylamine (48 mg, 0.5 mmol) in dry THF (4 mL) at 0 °C under a $N_2$ atmosphere. The solution was allowed to stir at 0 °C for 10 min and at room temperature for 30 min. The precipitated solids were removed by filtration and the filtrate was evaporated to dryness to afford a light-pink solid. Recrystallization from MeCN provided 55 mg (53%) of **23** as a white crystalline material, mp 142–143 °C (Table I).

Compounds **24** and **25** (Table I) were prepared in the same manner from **26** and **27**, respectively.

**Binding Studies.** The radioligand binding assay was conducted in essentially the same manner as reported earlier.[7] 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 one h and, following blot drying and weighing, were prepared and frozen at −30 °C until used. Freshly dissected (or frozen) tissue was homogenized in 30 vol 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 and Schuell) and were washed with 10 mL 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.[7] for greater detail.

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