**Kyung Ho Yoo,
Hyun Sik Choi,
Dong Chan Kim,
Kye Jung Shin,
Dong Jin Kim,
Yun Seon Song,
and Changbae Jin**

Division of Life Sciences,
Korea Institute of Science and
Technology, Seoul 130-650,
Korea

Synthesis of Heteroarylpiperazines and Heteroarylbipiperidines with a Restricted Side Chain and Their Affinities for 5-HT_{1A} Receptor

Heteroarylpiperazine and heteroarylbipiperidine derivatives, bearing a 4-piperidine ring instead of an alkylamino side chain to give the semi-rigidity, were prepared and evaluated for their abilities to displace [^{3}H] 8-OH-DPAT binding to the rat hippocampal synaptic membranes. These compounds showed low to moderate affinities for 5-HT_{1A} receptor, with Ki values ranging from 6912 nM to 232 nM. Of these compounds, **8 b** and **15 e** exhibited the best affinities for 5-HT_{1A} receptor with Ki values of 232 nM and 338 nM, respectively.

Keywords: Heteroarylpiperazines; Heteroarylbipiperidines; Restricted side chain; 5-HT_{1A} receptor affinities

Received: August 21, 2002; Accepted: January 6, 2003 [FP721]
DOI 10.1002/ardp.200300721

Introduction

The 5-HT_{1A} receptor subtype, among the large family of serotonin (5-HT) receptors, plays an important role in the central nerve system modulating a number of behaviors such as the regulation of mood, sleep, sexual behavior, food intake, anxiety, and depression [1–8]. During the last decade, the discovery of new ligands for 5-HT_{1A} receptor has been an area of active neurobiological research [9] because of its involvement in psychiatric disorders. The class of arylpiperazine derivatives as ligands at the 5-HT_{1A} receptor has been of great importance for studies into ligand-serotonin receptor interactions and is represented by buspirone [10].

In this study we carried out the chemical modification by the introduction of a restricted side chain to give the structural rigidity at 2-pyridine position of buspirone. To this end we attempted the replacement of a flexible aliphatic spacer with a piperidine ring and the introduction of bipiperidine moiety into heteroaromatic nucleus (Figure 1).

Here, we wish to report on the synthesis of the new classes of heteroarylpiperazines and heteroarylbipiperidines and their affinities for 5-HT_{1A} receptor. The most commonly used ligand 8-OH-DPAT [8-hydroxy-2-(*N,N*-di-*n*-propylamino)tetralin] [11–13] is a potent 5-HT_{1A} agonist, and the tritium-labeled compound is the ligand of choice for 5-HT_{1A} receptor-binding studies (K_d = 0.5 nM, rat hippocampal homogenates).

Correspondence: Kyung Ho Yoo, Division of Life Sciences, Korea Institute of Science and Technology, Seoul 130-650, Korea. E-mail: khyoo@kist.re.kr, Phone: +82 2 958-5152, Fax: +82 2 958-5189, e-mail: khyoo@kist.re.kr

Chemistry

2-[4-(*N*-Substituted-4-piperidinyl)-1-piperazinyl]pyrimidines **7–9** were prepared starting from *N*-benzyl-4-piperidinone (**1**) by the sequence of reactions shown in Scheme 1.

1 was debenzylated in the presence of Pearlmann's catalyst to give 4-piperidinone hydrochloride (**2**), which was then treated with the appropriate halide **3** in CH_3CN to afford the corresponding *N*-substituted-4-piperidinones **4–6**, respectively. Reductive amination of 4-piperidinone derivatives **4–6** with 1-(2-pyridyl)piperazine using sodium triacetoxyborohydride in CH_2Cl_2 gave the desired heteroarylpiperazines **7–9**.

The free base 2-(1-piperazinyl)pyrimidine (**11**), prepared from 2-(1-piperazinyl)-pyrimidine hydrochloride (**10**) under basic condition, was treated with 4-piperidinone derivatives **4–6** in the presence of sodium triacetoxyborohydride in CH_2Cl_2 to give the corresponding heteroarylpiperazines **7–9**, respectively (Scheme 2).

Other heteroarylpiperazine analogues **15–16** were prepared according to the route in Scheme 3. *N*-Phthalimidoethylpiperidinylpiperazines **15 a** and **15 b**, which were prepared from *N*-phthalimidoethyl-4-piperidinones (**6 d**) by the method described for the preparation of **7–9**, were deprotected with hydrazine hydrate to afford give the free amines **17 a** and **17 b** in excellent yields. Subsequently, **17 a** and **17 b** were converted to the corresponding heteroarylpiperazines **15** and **16** via *N*-alkylation, respectively.

On the other hand, heteroarylbipiperidines **20–22** were prepared by the route outlined in Scheme 4. The fluorine of 2-fluoropyridine (**18**) was replaced by 4,4′-bipiperidine group to give the bipiperidine **19**. Subsequent treat-

 0365-6233/04–05/0208 $ 17.50+.50/0

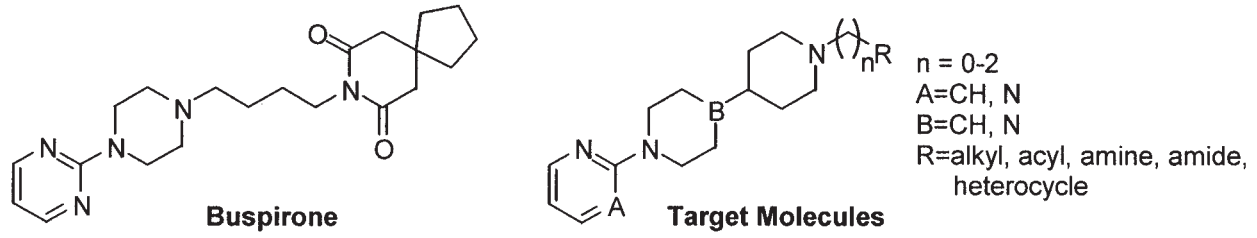
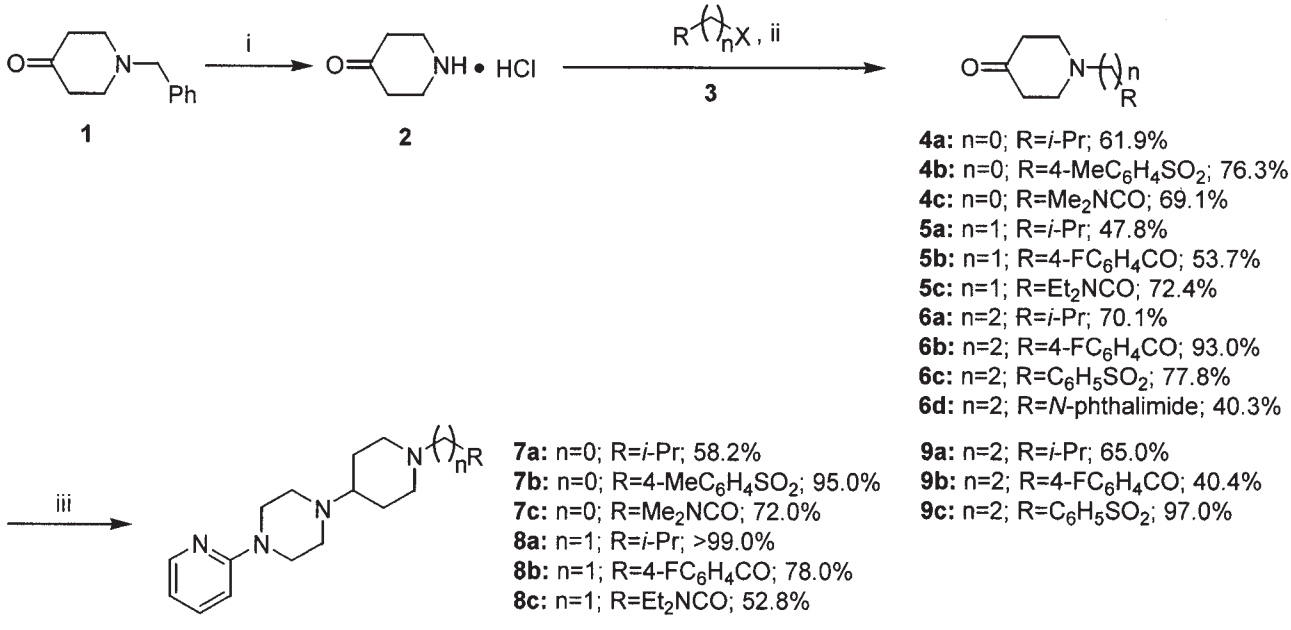
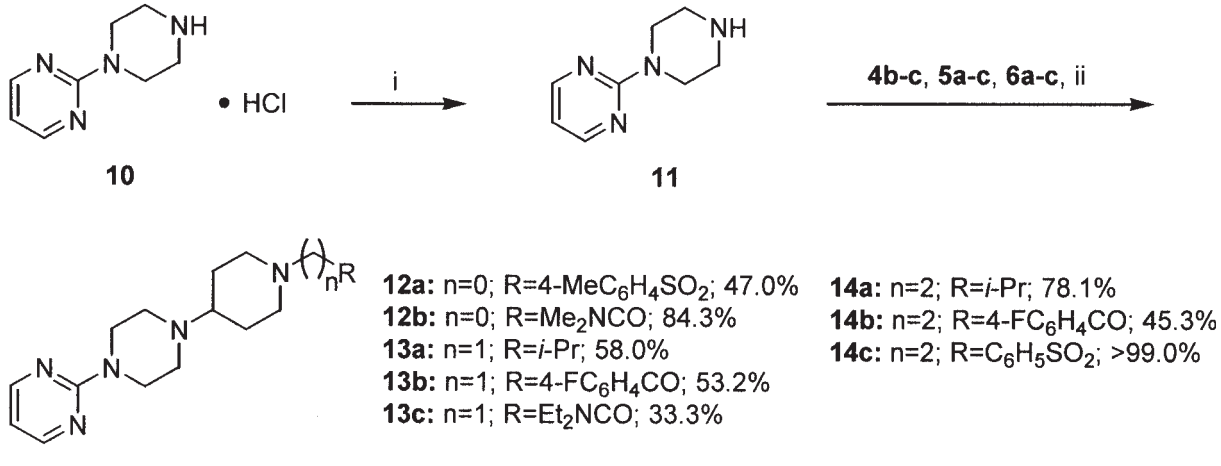


Figure 1. Structure of buspirone and target molecules.

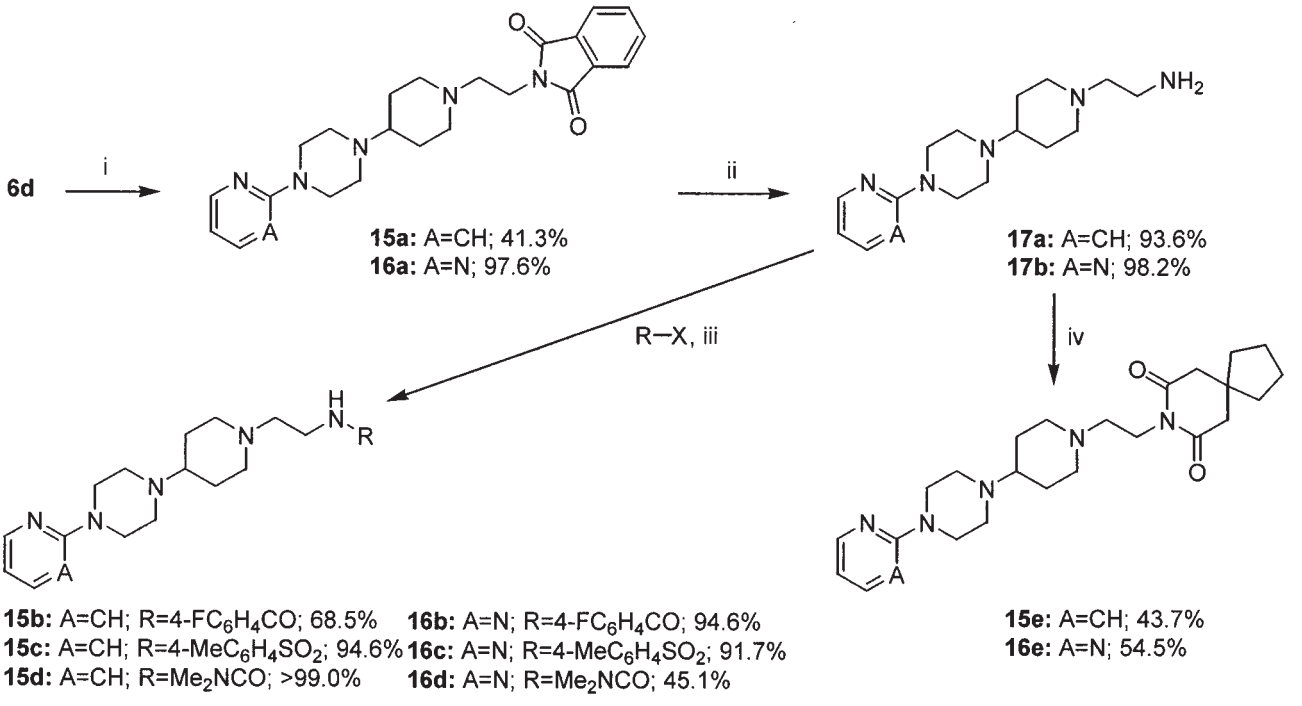


Scheme 1. Reagents and reaction conditions: (i) palladium hydroxide, 2*N* HCl, ab. EtOH, H_2/60 *psi*, rt, 24 h (97.0 %); (ii) K_2CO_3, CH_3CN, reflux or rt, 6–48 h; (iii) 1-(2-pyridyl)piperazine, sodium triacetoxyborohydride, AcOH, dichloromethane, rt, 12–15 h.

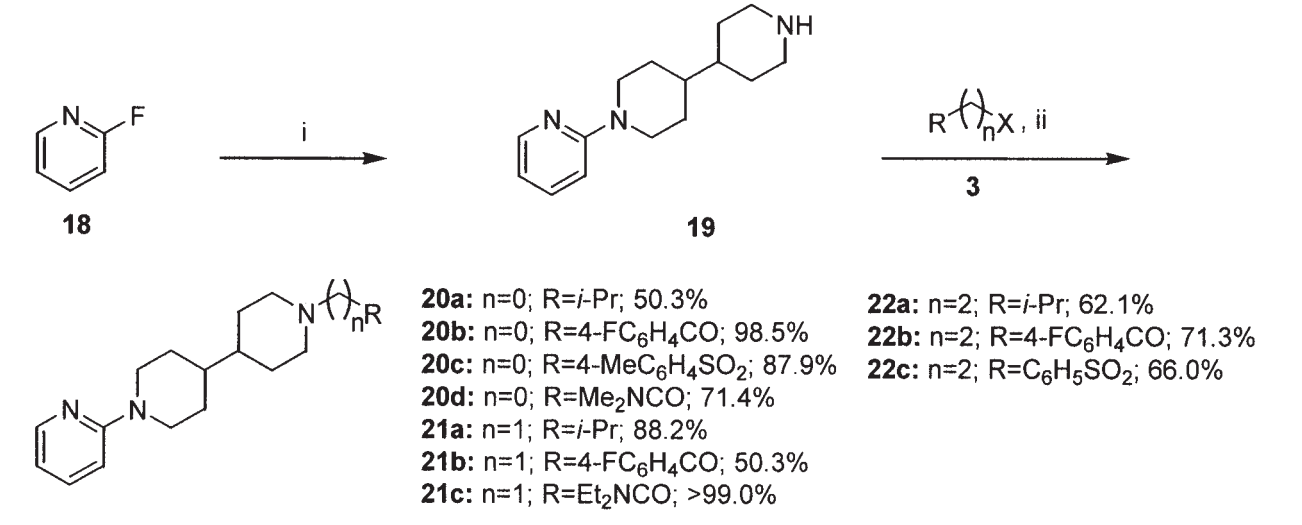


Scheme 2. Reagents and reaction conditions: (i) K_2CO_3, H_2O, rt, 2 h (75.2 %); (ii) sodium triacetoxyborohydride, AcOH, dichloromethane, rt, 12–15 h.

Full Paper



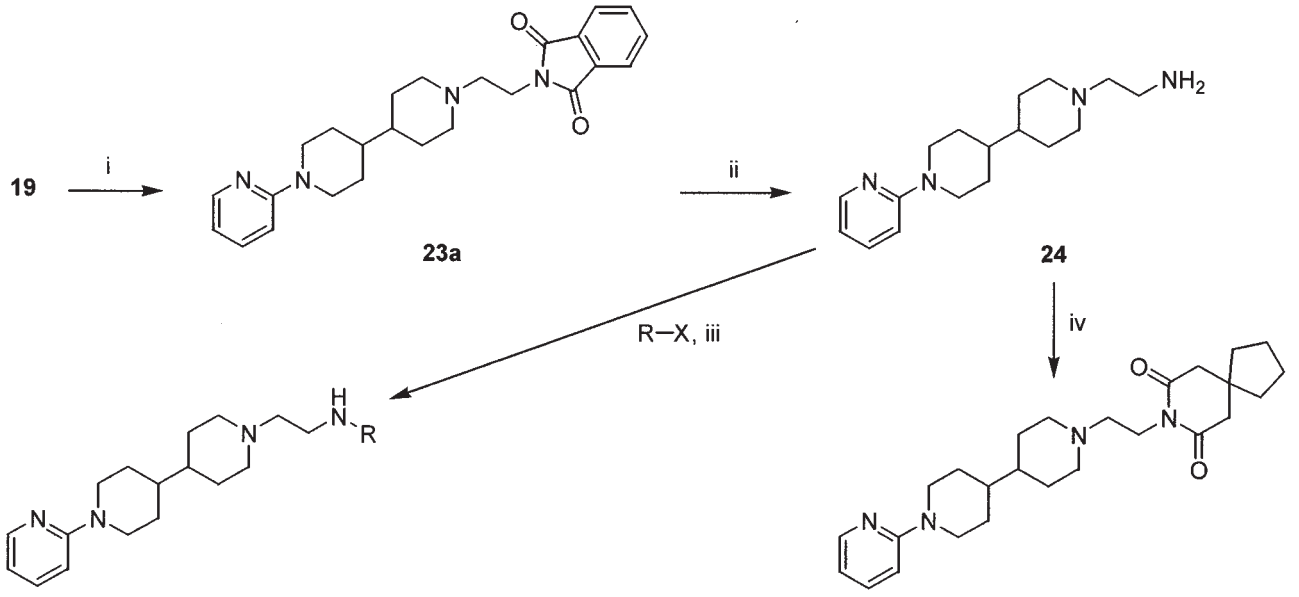
Scheme 3. Reagents and reaction conditions: (i) 1-(2-pyrdyl)piperazine (for **15 a**) or 1-(2-pyrimidyl)piperazine (for **16 a**), sodium triacetoxyborohydride, AcOH, dichloroethane, rt, 15 h; (ii) $N_2H_4 \cdot H_2O$, ab. MeOH, reflux, 2 h; (iii) Et_3N, THF or CH_2Cl_2, rt, 10–24 h; (iv) 3,3-tetramethyleneglutaric anhydride, xylene, reflux, 3 h.



Scheme 4. Reagents and reaction conditions: (i) 4,4′-bipiperidine dihydrochloride, $NaHCO_3$, ab. EtOH, reflux, 15 h (60.0 %); (ii) K_2CO_3 (or Et_3N), KI (for **21 c**, **22 b**), methylethylketone (or THF, CH_3CN), reflux or rt, 4–15 h.

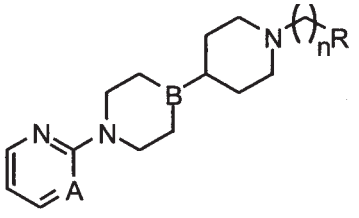
ment with the appropriate halide **3** under basic condition provided the corresponding heteroarylbipiperidines **20–22**, respectively.

Heteroarylbipiperidines **23** were prepared using the similar procedures for the preparation of **15** and **16** involving sequential *N*-alkylation by the bipiperidine **19**, deprotection of phthalimide group, and *N*-alkylation by the free amine **24** (Scheme 5).



Scheme 5. Reagents and reaction conditions: (i) *N*-bromoethylphthalimide, NaI, CH_3CN, reflux, 15 h (95.6 %); (ii) $N_2H_4 \cdot H_2O$, ab. MeOH, reflux, 3 h (83.4 %); (iii) Et_3N, THF or CH_2Cl_2 , rt, 10–24 h; (iv) 3,3-tetramethyleneglutaric anhydride, xylene, reflux, 15 h (97.2 %).

Table 1. 5-HT_{1A} receptor affinities of the selected compounds.



Compound	n	A	B	R	Ki (nM) ± SEM[a]
7 c	0	CH	N	Me_2NCO	1906 ± 103
8 a	1	CH	N	i-Pr	716 ± 81
8 b	1	CH	N	4-FC_6H_4CO	232 ± 18
8 c	1	CH	N	Et_2NCO	2640 ± 308
9 a	2	CH	N	i-Pr	2520 ± 142
9 b	2	CH	N	4-FC_6H_4CO	679 ± 23
9 c	2	CH	N	C_6H_5SO	22029 ± 185
13 b	1	N	N	4-FC_6H_4CO	3767 ± 209
15 b	2	CH	N	4-FC_6H_4CO	5125 ± 431
15 c	2	CH	N	4-MeC_6H_4CO	6912 ± 242
15 e	2	CH	N	8-azaspiro[4,5]decane-5,9-dione	338 ± 49
20 d	0	CH	CH	Me_2NCO	5194 ± 342
buspirone					47.2 ± 9.5
8-OH-DPAT					3.9 ± 0.9

[a] Ki values (± SEM) for displacement of [^{3}H] 8-OH-DPAT.

Biological Activity

Receptor binding data at 5-HT_{1A} for the selected compounds were illustrated in Table 1, along with those for buspirone and 8-OH-DPAT. Serotonergic 5-HT_{1A} receptor binding affinities were determined by displacement of [^{3}H] 8-OH-DPAT.

In our series, heteroarylpiperazine derivatives were more potent than the corresponding heteroarylbipiperidines. Among the synthesized compounds, heteroarylpiperazines **8 b** and **15 e** possessed the highest affinities for 5-HT_{1A} receptor (Ki = 232 nM and 338 nM). Compounds **8 a** and **9 b** exhibited the moderate affinities for 5-HT_{1A} receptor with Ki values of 716 nM and 679 nM, respectively. The 2-pyridine compounds as a heteroaromatic part displayed higher potency compared to the 2-pyrimidine compounds. Most 2-pyridine compounds didn't give any significant 5-HT_{1A} receptor affinity, except compound **13 b**.

Other variations such as the length of alkyl chains in spacer part and the size of substituents did n't not exhibited an appreciable difference for 5-HT_{1A} receptor binding affinity.

Acknowledgment

We are grateful to the Korea Institute of Science and Technology for financial support.

Experimental

Synthesis

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 16F PC FT-IR spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were obtained on a 300 MHz Bruker NMR spectrometer (300 MHz for ^{1}H and 75.5 MHz for ^{13}C) using tetramethylsilane as an internal standard. Microanalytical data were obtained by using an EA 1108 Fisons Instruments. Column chromatography was carried out using silica gel (230–400 mesh). Solvents and liquid reagents were transferred using hypodermic syringes. All other reagents and solvents used were reagent grade.

4-Piperidinone hydrochloride (**2**)

To a solution of *N*-benzyl-4-piperidinone (**1**, 1.00 g, 5.28 mmol) in EtOH (10 mL) were added Pearlmann's catalyst (0.15 g) and 2 *N* HCl (3 mL), and the mixture was sitrred stirred with H_2 (60 *psi*) at room temperature for 24 h. The catalyst was removed by filtration over celite and the solvent was removed from the filtrate. The residue was crystallized from petroleum ether to yield **2** as a dark yellow solid (0.62 g, 97.0 %): mp 95–97 °C; IR (KBr) 3312, 3202, 2978, 2800, 1722, 1572, 1414 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.34 (t, 4 H, *J* = 6.6 Hz), 2.60 (t, 4 H, *J* = 6.6 Hz); ^{13}C NMR (DMSO-d_6) δ 204.2, 90.6, 42.9.

General Procedure for the Preparation of N-Substituted-4-piperidinones (**4 a–c**, **5 a–c**, *and* **6 a–d**)

A suspension of **2** (2.00 mmol), the appropriate halide **3** (2.20 mmol), and an excess of K_2CO_3 (4.00 mmol) in CH_3CN (5 mL) was were stirred at room temperature (or refluxed) for 6–48 h. When the reaction was completed, the solvent was removed and the residue was treated with EtOAc and water. The organic layer was dried over anhydrous Na_2SO_4, and concentrated *in vacuoin vacuum*. The residue was purified by silica gel column chromatography to yield the title compound.

N-(N′,N′-Dimethylcarbamoyl)-4-piperidinone (**4 c**)

Yield 69.1 %; mp 50–52 °C; IR (KBr) 2913, 1711, 1650, 1630, 1500, 1453, 1400 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.46 (t, 4 H, *J* = 6.1 Hz), 2.83 (s, 6 H), 2.42 (t, 4 H, *J* = 6.1 Hz); ^{13}C NMR ($CDCl_3$) δ 208.3, 164.6, 46.7, 41.7, 38.9.

N-(N′,N′-Diethylcarbamoylmethylene)-4-piperidinone (**5 c**)

Yield 72.4 %; oil; IR (NaCl) 3498, 2970, 2808, 1714, 1632, 1470 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.38 (m, 4 H), 3.32 (s, 2 H), 2.83 (t, 4 H, *J* = 5.9 Hz), 2.47 (t, 4 H, *J* = 5.9 Hz), 1.17 (t, 3 H, *J* = 7.0 Hz), 1.11 (t, 3 H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$) d 208.9, 168.6, 59.7, 53.6, 42.0, 41.5, 40.5, 14.7, 13.2.

N-Benzenesulfonylethylene-4-piperidinone (**6 c**)

Yield 77.8 %; mp 132–133 °C; IR (KBr) 3422, 2963, 2812, 1714, 1298 cm^{-1}; ^{1}H NMR ($CDCl_3$) d 7.96–7.58 (m, 5 H), 3.34 (t, 2 H, *J* = 7.3 Hz), 2.91 (t, 2 H, *J* = 7.3 Hz), 2.66 (t, 4 H, *J* = 5.9 Hz), 2.30 (t, 4 H, *J* = 5.9 Hz); ^{13}C NMR ($CDCl_3$) δ 208.2, 140.3, 134.1, 129.6, 128.4, 54.4, 53.0, 50.9, 41.2.

General Procedure for the Preparation of 2-[4-(N-Substituted-4-piperidinyl)-1-piperazinyl]pyridines (**7 a–c**, **8 a–c**, *and* **9 a–c**)

To a solution of 2-(1-piperazinyl)pyridine (1.00 mmol) and the appropriate compound **4 a–c**, **5 a–c**, **6 a–c** (1.10 mmol) in CH_2Cl_2 (10 mL) wereas added acetic acid (0.06 mL) and sodium triacetoxyborohydride (1.50 mmol), and the mixture was stirred at room temperature for 12–15 h. The mixture was concentrated *in vacuum* and the residue partitioned between saturated aqueous $NaHCO_3$ and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with brine and the solvent removed *in vacuum*. The residue was purified by silica gel column chromatography to yield the title compound as a solid.

2-[4-[N-(N′,N′-Dimethylcarbamoyl)-4-piperidinyl]-1-piperazinyl]pyridine (**7 c**)

Yield 72.0 %; mp 117–118 °C; IR (KBr) 3440, 2842, 1638, 1596, 1482, 1440, 1394 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.12 (d, 1 H, *J* = 4.1 Hz), 7.42 (t, 1 H, *J* = 7.9 Hz), 6.57 (m, 2 H), 4.72 (m, 2 H), 3.65 (m, 2 H), 3.47 (t, 4 H, *J* = 4.9 Hz), 3.42 (m, 1 H), 2.75 (s, 6 H), 2.70 (m, 2 H), 2.63 (t, 4 H, *J* = 4.9 Hz), 1.80 (m, 2 H); ^{13}C NMR ($CDCl_3$) d 165.3, 159.9, 148.3, 137.8, 113.7, 107.4, 62.5, 49.4, 46.7, 45.9, 38.9, 28.7. Anal. Calcd for $C_{17}H_{27}N_{5O}$: C, 64.32; H, 8.57; N, 22.06. Found: C, 64.46; H, 8.76; N, 21.96.

2-[4-[N-(N′,N′-Diethylcarbamoylmethylene)-4-piperidinyl]-1-piperazinyl]pyridine (**8 c**)

Yield 52.8 %; mp 96–97 °C; IR (KBr) 3496, 2932, 2824, 1620, 1482, 1440 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.18 (d, 1 H, *J* = 3.8 Hz), 7.47 (t, 1 H, *J* = 4.7 Hz), 6.23 (m, 2 H), 3.56 (t, 4 H, *J* = 4.9 Hz), 3.37 (m, 4 H), 3.15 (s, 2 H), 3.00 (m, 2 H), 2.69 (t, 4 H, *J* = 4.9 Hz), 2.31 (m, 1 H), 2.10 (t, 2 H, *J* = 11.3 Hz), 1.85 (m, 2 H), 1.63 (m, 2 H), 1.14 (m, 6 H); ^{13}C NMR ($CDCl_3$) d 169.2, 159.9, 148.3, 137.8, 113.6, 107.4, 62.1, 61.6, 53.7, 49.4, 45.9, 42.1, 40.4, 28.6, 14.7, 13.3. Anal. Calcd for $C_{20}H_{33}N_{5O}$: C, 66.82; H, 9.25; N, 19.48. Found: C, 66.88; H, 9.33; N, 19.13.

2-[4-[N-Benzenesulfonylethylene-4-piperidinyl]-1-piperazinyl]pyridine (**9 c**)

Yield 97.0 %; mp 158–159 °C; IR (KBr) 3436, 2946, 2762, 1592, 1479, 1440 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.18 (d, 1H, *J* = 4.6 Hz), 7.91 (d, 2 H, *J* = 7.4 Hz), 7.65–7.43 (m, 4 H), 6.62 (m, 2 H), 3.51 (t, 4 H, *J* = 5.0 Hz), 3.30 (t, 2 H, *J* = 7.7 Hz), 2.76 (m, 4 H), 2.62 (t, 4 H, *J* = 5.0 Hz), 2.22 (m, 1 H), 1.96 (t, 2 H, *J* = 7.7 Hz), 1.73 (m, 2 H), 1.37 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 159.9, 148.3, 140.1, 137.8, 134.0, 129.6, 128.4, 113.6, 107.4, 62.0, 54.2, 53.2, 51.6, 49.3, 45.9, 28.2. Anal. Calcd for $C_{22}H_{30}N_4O_2S$: C, 63.74; H, 7.29; N, 13.51. Found: C, 63.50; H, 7.40; N, 13.67.

2-(1-Piperazinyl)pyrimidine (**11**)

To a stirred solution of 2-(1-piperazinyl)pyrimidine hydrochloride **10** (1.00 g, 4.20 mmol) in water (10 mL) was added saturated aqueous K_2CO_3. After being stirred at room temperature for 2 h, the mixture was diluted with EtOAc and water. The organic layer was dried over anhydrous Na_2SO_4, and concentrated *in vacuum* to yield **11** as a yellow oil (0.52 g, 75.2 %): IR (NaCl) 3440, 2994, 2844, 1596, 1484, 1438 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.22 (m, 2 H), 6.39 (m, 1 H), 3.71 (t, 4 H, *J* = 5.1 Hz), 2.85 (t, 4 H, *J* = 5.1 Hz), 1.98 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 161.5, 158.0, 110.0, 46.2, 45.1.

General Procedure for the Preparation of 2-[4-(N-Substituted-4-piperidinyl)-1-piperazinyl]pyrimidines (**12 a**, **b**, **13 a–c**, *and* **14 a–c**)

To a solution of 2-(1-piperazinyl)pyrimidine (1.00 mmol), the appropriate compound **4 b–c**, **5 a–c**, **6 a–c** (1.10 mmol), acetic acid (0.06 mL), and sodium triacetoxyborohydride (1.5 mmol) in CH_2Cl_2 (10 mL) were stirred at room temperature for 12–15 h. The solvent was evaporated *in vacuum* and the residue partitioned between saturated aqueous $NaHCO_3$ and CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4, evaporated *in vacuum*. The residue was purified by silica gel column chromatography to yield the title compound as a solid.

2-[4-[N-(N′,N′-Dimethylcarbamoyl)-4-piperidinyl]-1-piperazinyl]-pyrimidine (**12 b**)

Yield 84.3 %; mp 110–111 °C; IR (KBr) 3476, 2968, 2856, 1632, 1490, 1366 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.23 (d, 2 H, *J* = 4.7 Hz), 6.41 (t, 1 H, *J* = 4.8 Hz), 3.75 (t, 4 H, *J* = 5.2 Hz), 3.65 (m, 2 H), 2.75 (s, 6 H), 2.71 (t, 2 H, *J* = 11.3 Hz), 2.56 (t, 4 H, *J* = 5.2 Hz), 2.35 (m, 1 H), 1.79 (m, 2 H), 1.47 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 165.3, 162.0, 158.1, 110.2, 62.6, 49.4, 46.7, 44.4, 38.9, 28.7. Anal. Calcd for $C_{16}H_{26}N_{6O}$: C, 60.35; H, 8.23; N, 26.39. Found: C, 60.63; H, 8.43; N, 26.21.

2-[4-[N-(4-Fluorobenzoylmethylene)-4-piperidinyl]-1-piperazinyl]pyrimidine (**13 b**)

Yield 53.2 %; mp 123–124 °C; IR (KBr) 3434, 2928, 2788, 1692, 1588, 1448 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.29 (d, 2H, *J* = 4.7 Hz), 8.07 (m, 2 H), 7.13 (m, 2 H), 6.47 (t, 1 H, *J* = 4.7 Hz), 3.83 (t, 4 H, *J* = 5.0 Hz), 3.74 (s, 2 H), 3.04 (m, 2 H), 2.64 (t, 4 H, *J* = 5.0 Hz), 2.36 (m, 1 H), 2.17 (t, 2 H, *J* = 11.3 Hz), 1.83 (m, 2 H), 1.72 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 195.6, 167.8, 164.4, 158.1, 131.3, 116.1, 115.8, 110.2, 65.0, 62.0, 53.8, 49.2, 44.1, 28.2. Anal. Calcd for $C_{21}H_{26}FN_5O$: C, 65.78; H, 6.83; N, 18.26. Found: C, 65.83; H, 6.74; N, 17.90.

2-[4-[N-(4-Fluorobenzoylethylene)-4-piperidinyl]-1-piperazinyl]pyrimidine (**14 b**)

Yield 45.3 %; mp 105–106 °C; IR (KBr) 3427, 3186, 1676, 1590, 1464, 1401 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.30 (d, 2H, *J* = 4.7 Hz), 7.99 (m, 2 H), 7.13 (t, 2 H, *J* = 8.6 Hz), 6.47 (m, 1 H), 3.83 (m, 4 H), 3.16 (t, 2 H, *J* = 7.4 Hz), 3.02 (m, 2 H), 2.81 (t, 2 H, *J* = 7.4 Hz), 2.62 (m, 4 H), 2.33 (m, 1 H), 2.06 (t, 2 H, *J* = 11.3 Hz), 1.86–1.58 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 198.0, 162.0, 158.1, 131.1, 131.0, 116.2, 116.0, 110.1, 62.4, 53.8, 53.5, 49.4, 44.4, 37.0, 28.5. Anal. Calcd for $C_{22}H_{28}FN_5O$: C, 66.48; H, 7.10; N, 17.62. Found: C, 66.65; H, 7.30; N, 17.22.

General Procedure for the Preparation of 2-[4-(N-Phthalimidoethyl-4-piperidinyl)-1-piperazinyl]pyridine (or pyrimidine) (**15 a** *and* **16 a**)

2-(1-Piperazinyl)pyridine (or pyrimidine) (1.00 mmol) was stirred at room temperature with *N*-phthalimidoethyl-4-piperidinone **6 d** (1.10 mmol) and sodium triacetoxyborohydride (1.50 mmol) containing acetic acid (0.06 mL) in CH_2Cl_2 (10 mL) for 15 h. The mixture was treated with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2, and the organic layers were washed with saturated aqueous $NaHCO_3$ and water, dried over anhydrous Na_2SO_4, and evaporated *in vacuum*. The residue was purified by silica gel column chromatography to yield the title compound as a solid.

2-[4-(N-Phthalimidoethyl-4-piperidinyl)-1-piperazinyl]-pyrimidine (**16 a**)

Yield 97.6 %; mp 178–180 °C; IR (KBr) 3455, 2947, 2820, 1710, 1584, 1496, 1396 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.29 (d, 2 H, *J* = 4.7 Hz), 7.83 (m, 2 H), 7.72 (m, 2 H), 6.47 (t, 1 H, *J* = 4.7 Hz), 3.81 (m, 6 H), 3.05 (m, 2 H), 2.61 (m, 6 H), 2.24 (m, 1 H), 2.02 (t, 2 H, *J* = 11.2 Hz), 1.80 (m, 2 H), 1.50 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 168.7, 162.0, 158.1, 134.2, 132.6, 123.5, 110.1, 62.4, 55.9, 53.5, 49.5, 44.4, 36.0, 28.7. Anal. Calcd for $C_{23}H_{28}N_6O_2$: C, 65.69; H, 6.71; N, 19.99. Found: C, 65.73; H, 6.66; N, 19.58.

General Procedure for the Preparation of 2-[4-(N-Aminoethyl-4-piperidinyl)-1-piperazinyl]pyridine (or pyrimidine) (**17 a**, **b**)

A mixture of the appropriate compound **15 a**, **16 a** (0.25 mmol) and hydrazine hydrate (0.38 mmol) in MeOH (5 mL) was stirred under reflux for 2 h. After cooling, the reaction mixture was filtered and evaporated. Dissolution of the residue in 1 *M* NaOH, extraction with EtOAc, drying and evaporation yielded the title compound as a solid.

2-[4-(N-Aminoethyl-4-piperidinyl)-1-piperazinyl]pyrimidine (**17 b**)

Yield 98.2 %; mp 76–78 °C; IR (KBr) 3358, 2822, 1586, 1550, 1482 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.33 (d, 2 H, *J* = 4.7 Hz), 6.60 (t, 1 H, *J* = 4.7 Hz), 3.69 (t, 4 H, *J* = 4.9 Hz), 2.87 (m, 2 H), 2.78 (t, 2 H, *J* = 6.2 Hz), 2.51 (t, 4 H, *J* = 4.9 Hz), 2.39 (t, 2 H, *J* = 6.2 Hz), 2.24 (m, 1 H), 1.89 (t, 2 H, *J* = 11.2 Hz), 1.72 (m, 2 H), 1.44 (m, 2 H); ^{13}C NMR (DMSO-d_6) δ 162.0, 158.7, 110.8, 62.3, 61.6, 53.8, 49.5, 44.5, 28.8. Anal. Calcd for $C_{15}H_{26}N_6$: C, 62.04; H, 9.02; N, 28.94. Found: C, 62.06; H, 9.43; N, 28.89.

General Procedure for the Preparation of 2-[4-[N-(N′-Substituted aminoethyl)-4-piperidinyl]-1-piperazinyl]pyridine (or pyrimidine) (**15 b–d** *and* **16 b–d**)

To aminoethyl compound **17 a**, **b** (0.50 mmol) in THF (or CH_2Cl_2) (5 mL) were added the appropriate halide (1.00 mmol) and Et_3N (3.50 mmol). The solution was stirred at room temperature for 24 h, and then the solvent was evaporated under reduced pressure. To the remainder was added EtOAc, washed with water, dried and evaporated under reduced pressure. The residue was purified by silica gel column chromatography to yield the title compound as a solid.

2-[4-[N-[N′-(4-Methylbenzenesulfonyl)]aminoethyl]-4-piperidinyl]piperazinyl]pyridine (**15 c**)

Yield 94.6 %; mp 138–140 °C; IR (KBr) 3284, 2924, 2844, 1594, 1476, 1436 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.12 (d, 1H, *J* = 3.7 Hz), 7.70 (m, 2 H), 7.43 (t, 1 H, *J* = 7.1 Hz), 7.24 (m, 2 H), 6.60 (m, 2 H), 3.73 (m, 4 H), 3.06 (m, 4 H), 2.97 (m, 2 H), 2.84 (m, 4 H), 2.64 (m, 2 H), 2.36 (s, 3 H), 2.27 (m, 1 H), 2.01 (m, 2 H), 1.87 (m, 2 H); ^{13}C NMR ($CDCl_3$) d 159.9, 148.4, 143.7, 137.8, 137.5, 130.0, 127.5, 113.7, 107.4, 62.1, 55.8, 52.9, 49.4, 46.0, 39.9, 28.6, 21.9. Anal. Calcd for $C_{23}H_{33}N_5O_2S$: C, 62.27; H, 7.50; N, 15.79. Found: C, 62.41; H, 7.40; N, 15.37.

2-[4-[N-[N′-(4-Methylbenzenesulfonyl)]aminoethyl]-4-piperidinyl]piperazinyl]-pyrimidine (**16 c**)

Yield 91.7 %; mp 165–166 °C; IR (KBr) 3252, 2952, 2822, 1738, 1584, 1548, 1476, 1446, 1416 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.25 (d, 2 H, *J* = 4.7 Hz), 7.70 (m, 2 H), 7.24 (m, 2 H), 6.47 (t, 1 H, *J* = 4.7 Hz), 4.02 (m, 4 H), 3.04 (m, 4 H), 2.90 (m, 2 H), 2.73 (m, 4 H), 2.36 (m, 2 H), 2.35 (s, 3 H), 2.21 (m, 1 H), 1.96 (m, 2 H), 1.77 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 162.0, 158.1, 143.7, 137.0, 130.0, 127.5, 110.2, 62.2, 55.8, 52.9, 49.5, 44.4, 39.9, 28.6, 21.9. Anal. Calcd for $C_{22}H_{32}N_6O_2S$: C, 59.43; H, 7.25; N, 18.90. Found: C, 59.42; H, 7.38; N, 18.84.

General Procedure for the Preparation of 2-[4-[N-[(8-azaspiro-[4,5]decane-7,9-dionyl)-8-ethyl]-4-piperidinyl]-1-piperazinyl]pyridine (or pyrimidine) (**15 e** *and* **16 e**)

3,3-Tetramethylene glutaric anhydride (0.55 mmol) was combined with aminoethyl compound **17 a**, **b** (0.50 mmol) in xylene (10 mL), and the mixture was heated to reflux with Dean Stark trap until the theoretical amount of water was removed. The reaction mixture was then cooled and diluted with EtOAc. The resulting solution was washed with brine, dried over $MgSO_4$, and evaporated to dryness. The residue was purified by silica gel column chromatography to yield the title compound as a solid.

2-[4-[N-[(8-Azaspiro[4,5]decane-7,9-dionyl)-8-ethyl]-4-piperidinyl]-1-piperazinyl]-pyrimidine (**16 e**)

Yield 54.5 %; mp 129–130 °C; IR (KBr) 3045, 2932, 2858, 2808, 1726, 1676, 1584, 1546, 1488, 1448 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.29 (d, 2 H, *J* = 4.7 Hz), 6.47 (t, 1 H, *J* = 4.7 Hz), 3.91 (t, 2 H, *J* = 6.7 Hz), 3.82 (m, 4 H), 3.01 (m, 2 H), 2.60 (m, 8 H), 2.44 (t, 2 H, *J* = 6.7 Hz), 2.32 (m, 1 H), 1.99 (t, 2 H, *J* = 11.3 Hz), 1.81–1.69 (m, 6 H), 1.54–1.52 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 172.5, 162.4, 158.1, 110.1, 62.5, 55.7, 53.7, 49.4, 45.2, 44.4, 39.9, 37.8, 37.1, 28.6, 24.5. Anal. Calcd for $C_{24}H_{36}N_6O_2$: C, 65.43; H, 8.24; N, 19.07. Found: C, 65.73; H, 8.22; N, 19.02.

2-[(4,4′-Bipiperidin)-1-yl]pyridine (**19**)

A mixture of 2-fluoropyridine **18** (0.39 g, 4.00 mmol), 4,4′-bipiperidine dihydrochloride (0.48 g, 2.00 mmol), and $NaHCO_3$ (0.76 g, 9.0 mmol) in EtOH (5 mL) was stirred under reflux for 15 h. After cooling, the solvent was removed *in vacuum* and the residue was extracted with EtOAc and washed with water. The organic extracts were dried over anhydrous Na_2SO_4, and the solvent was removed. The residue was purified by silica gel column chromatography using as eluent a mixture of CH_2Cl_2:MeOH:NH_4OH (5:4:1) to yield **19** as a white solid (0.30 g, 60.0 %): mp 148–150 °C; IR (KBr) 3430, 2948, 2843, 1574, 1516, 1485, 1436 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.15 (d, 1H, *J* = 3.7 Hz), 7.43 (m, 1 H), 6.65–6.53 (m, 2 H), 4.30 (m, 2 H), 3.08 (m, 2 H), 2.74 (t, 2 H, *J* = 10.8 Hz), 2.55 (t, 2 H, *J* = 10.8 Hz), 2.05 (m, 1 H), 1.78 (d, 2 H, *J* = 7.4 Hz), 1.68 (d, 2 H, *J* = 7.4 Hz), 1.27–1.18 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 148.6, 138.4, 113.3, 108.0, 95.5, 46.5, 46.1, 41.9, 29.7, 29.3.

General Procedure for the Preparation of 1-Substituted-1′-(2-pyridyl)-4,4′-bipiperidine (**20 a–d**, **21 a–c**, *and* **22 a–c**)

To a solution of bipiperidinylpyridine **19** (0.50 mmol) and the appropriate halide **3** (1.00 mmol) in methylethylketone (or THF, CH_3CN) (5 mL) was were added K_2CO_3 (1.75 mmol) and a catalytic amount of KI (for **21 c**, **22 b**), and the mixture was stirred at room temperature (or refluxed) for 4–15 h. When the reaction was completed, the solvent was removed *in vacuum* and the residue was extracted with CH_2Cl_2 and washed with water. The organic extracts were dried over anhydrous Na_2SO_4, and the solvent was removed. The residue was purified by silica gel column chromatography to yield the title compound as a solid.

1-(4-Methylbenzenesulfonyl)-1′-(2-pyridyl)-4,4′-bipiperidine (**20 c**)

Yield 87.9 %; mp 226–228 °C; IR (KBr) 3432, 2948, 2846, 1592, 1472, 1436 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.18 (m, 1 H), 7.56 (m, 2 H), 7.29 (m, 2 H), 6.66–6.56 (m, 2 H), 4.30 (m, 2 H), 3.84 (m, 2 H), 2.75 (t, 2 H, *J* = 12.1 Hz), 2.45 (s, 3 H), 2.17 (td, 2 H, *J* = 11.9, 2.3 Hz), 1.78 (m, 4 H), 1.44–1.24 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 146.4, 143.7, 138.7, 133.1, 129.8, 128.0, 112.8, 108.1, 98.3, 46.9, 46.3, 40.8, 40.4, 29.1, 28.9, 21.8. Anal. Calcd for $C_{22}H_{29}N_3O_2S$: C, 66.13; H, 7.32; N, 10.52. Found: C, 66.14; H, 7.43; N, 10.65.

1-(N,N-Diethylcarbamoylmethylene)-1′-(2-pyridyl)-4,4′-bipiperidine (**21 c**)

Yield >99.0 %; mp 157–160 °C; IR (KBr) 3468, 2940, 2822, 1632, 1478, 1438, 1380 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.10 (d, 1H, *J* = 3.4 Hz), 7.38 (t, 1 H, *J* = 6.0 Hz), 6.60–6.50 (m, 2 H), 4.23 (m, 2 H), 4.08 (m, 1 H), 3.39–3.26 (m, 6 H), 3.09 (m, 1 H), 2.95 (m, 2 H), 2.66 (t, 2 H, *J* = 12.2 Hz), 1.71 (m, 4 H), 1.38 (m, 2 H), 1.24–1.03 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 168.8, 159.8, 148.1, 137.6, 112.8, 107.4, 61.3, 54.4, 46.1, 41.9, 41.3, 40.6, 40.2, 29.4, 29.3, 14.5, 13.1. Anal. Calcd for $C_{21}H_{34}N_4O$: C, 70.35; H, 9.56; N, 15.63. Found: C, 70.34; H, 79.65; N, 14.85.

1-(4-Benzenesulfonylethylene)-1′-(2-pyridyl)-4,4′-bipiperidine (**22 c**)

Yield 66.0 %; mp 121–122 °C; IR (KBr) 3433, 2940, 2839, 1594, 1478, 1438 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.19 (m, 1 H), 8.16 (m, 2 H), 7.66 (m, 1 H), 7.59 (m, 2 H), 7.46 (m, 1 H), 6.67–6.56 (m, 2 H), 4.31 (m, 2 H), 3.36 (t, 2 H, *J* = 7.0 Hz), 2.75 (m, 6 H), 2.66 (t, 2 H, *J* = 12.2 Hz), 2.00 (m, 2 H), 1.75 (m, 2 H), 1.66 (m, 2 H), 1.30–1.06 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 160.0, 148.4, 140.2, 137.7, 134.0, 129.5, 128.4, 113.0, 107.5, 54.2, 54.1, 51.9, 46.2, 41.5, 40.9, 29.5, 29.4. Anal. Calcd for $C_{23}H_{31}N_3O_2S$: C, 66.79; H, 7.56; N, 10.16. Found: C, 66.56; H, 7.76; N, 10.25.

1-Phthalimidoethyl-1′-(2-pyridyl)-4,4′-bipiperidine (**23 a**)

To a stirred solution of bipiperidinylpyridine **19** (0.50 mmol) and *N*-bromoethylphthalimide (1.00 mmol) in CH_3CN (10 mL) was were added K_2CO_3 (1.75 mmol) and NaI (0.10 mmol), and the mixture was heated at reflux for 15 h. The solvent was removed and the residue was treated with CH_2Cl_2 and water. The aqueous layer was separated and extracts were washed with water, dried over anhydrous Na_2SO_4, and evaporated to dryness to yield a residue. The residue was purified by silica gel column chromatography using as eluent a mixture of CH_2Cl_2:MeOH:NH_4OH (5:4:1) to yield **23 a** as a yellow solid (0.20 g, 95.6 %): mp 196–197 °C; IR (KBr) 2948, 2816, 1770, 1708, 1594, 1480, 1436, 1400 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.17 (d, 1 H, *J* = 3.3 Hz), 7.86 (m, 2 H), 7.73 (m, 2 H), 7.44 (m, 1 H), 6.67–6.55 (m, 2 H), 4.30 (m, 2 H), 3.84 (t, 2 H, *J* = 6.9 Hz), 3.04 (m,

2 H), 2.75 (t, 2 H, *J* = 11.7 Hz), 2.62 (t, 2 H, *J* = 6.9 Hz), 1.98 (t, 2 H, *J* = 11.0 Hz), 1.81–1.68 (m, 4 H), 1.27–1.19 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 168.5, 148.3, 137.7, 134.2, 132.6, 123.5, 112.9, 107.4, 103.3, 56.3, 54.4, 46.3, 41.5, 41.0, 35.8, 29.7, 29.4.

1-Aminoethyl-1′-(2-pyridyl)-4,4′-bipiperidine (**24**)

A mixture of phthalimidoethyl compound **23 a** (0.25 mmol) and hydrazine hydrate (0.38 mmol) in MeOH (5 mL) was stirred under reflux for 3 h. After cooling, the reaction mixture was filtered and evaporated. Dissolution of the residue in 1 *M* NaOH, extraction with EtOAc, drying and evaporation yielded the residue. The residue was purified by silica gel column chromatography using as eluent a mixture of CH_2Cl_2:MeOH:NH_4OH (20:4:1) to yield **24** as a pale yellow solid (0.06 g, 83.4 %): mp 93–94 °C; IR (KBr) 3418, 2944, 2838, 1598, 1486 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.10 (m, 1 H), 7.36 (m, 1 H), 6.60–6.47 (m, 2 H), 4.23 (m, 2 H), 2.88 (m, 2 H), 2.80 (t, 2 H, *J* = 6.2 Hz), 2.68 (t, 2 H, *J* = 11.7 Hz), 2.39 (t, 2 H, *J* = 6.2 Hz), 1.89 (t, 2 H, *J* = 10.6 Hz), 1.74–1.63 (m, 4 H), 1.28–1.17 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 155.4, 143.7, 133.1, 108.3, 102.9, 56.6, 50.1, 41.7, 36.9, 36.6, 34.5, 25.2, 24.8.

General Procedure for the Preparation of 1-(N-Substituted aminoethyl)-1′-(2-pyridyl)-4,4′-bipiperidine (**23 b–d**)

To aminoethyl compound **24** (0.50 mmol) in THF (or CH_2Cl_2) (5 mL) were added the appropriate halide (1.00 mmol) and Et_3N (3.50 mmol). The solution was stirred at room temperature for 10–24 h, and then the solvent was evaporated under reduced pressure. To the remainder was added EtOAc, washed with water, dried and evaporated under reduced pressure. The residue was purified by silica gel column chromatography to yield the title compound as a solid.

1-[N-(4-Methylbenzenesulfonyl)aminoethyl]-1′-(2-pyridyl)-4,4′-bipiperidine (**23 c**)

Yield >99.0 %; mp 124–125 °C; IR (KBr) 3290, 2926, 2841, 1596, 1480, 1436 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.17 (d, 1 H, *J* = 3.3 Hz), 7.75 (m, 2 H), 7.45 (m, 1 H), 7.30 (m, 2 H), 6.67–6.57 (m, 2 H), 4.30 (m, 2 H), 2.97 (m, 2 H), 2.76 (t, 2 H, *J* = 11.6 Hz), 2.75 (m, 2 H), 2.42 (s, 3 H), 2.36 (m, 2 H), 1.81 (m, 4 H), 1.63 (m, 2 H), 1.25–1.13 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 155.7, 147.7, 139.6, 133.7, 130.3, 128.5, 112.9, 108.9, 98.6, 56.9, 50.4, 42.0, 37.3, 36.8, 34.7, 25.9, 24.9, 21.9. Anal. Calcd for $C_{24}H_{34}N_4O_2S$: C, 65.13; H, 7.74; N, 12.66. Found: C, 64.50; H, 7.73; N, 11.47.

1-[(8-Azaspiro[4,5]decane-7,9-dionyl)-8-ethyl]-1′-(2-pyridyl)-4,4′-bipiperidine (**23 e**)

3,3-Tetramethylene glutaric anhydride (0.55 mmol) was combined with aminoethyl compound **24** (0.50 mmol) in xylene (10 mL), and the mixture was heated to reflux with Dean Stark trap until the theoretical amount of water was removed. The reaction mixture was then cooled and diluted with EtOAc. The resulting solution was washed with brine, dried over $MgSO_4$, and evaporated to dryness. The residue was purified by silica gel column chromatography using as eluent a mixture of EtOAc:MeOH (3:1) to yield **23 e** as a dark yellow solid (0.21 g, 97.2 %): mp 141–143 °C; IR (KBr) 3436, 2946, 2814, 1727, 1674, 1592, 1436 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.10 (d, 1 H, *J* = 3.5 Hz), 7.38 (m, 1 H), 6.59–6.47 (m, 2 H), 4.23 (m, 2 H), 3.87 (m, 2 H), 2.92 (m, 2 H), 2.68 (t, 2 H, *J* = 11.7 Hz), 2.54 (s, 4 H), 2.39 (m, 2 H), 1.98 (m, 2 H), 1.73–1.61 (m, 8 H), 1.44 (t, 4 H, *J* = 6.6 Hz), 1.17 (d, 4 H, *J* = 5.3 Hz), 1.03 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 172.2, 159.6, 148.0, 137.3, 112.5, 107.1, 55.7, 54.3, 45.9, 44.9, 41.3, 40.8, 39.5, 37.5, 36.8, 29.5, 29.1, 24.1. Anal. Calcd for $C_{26}H_{38}N_4O_2$: C, 71.20; H, 8.73; N, 12.77. Found: C, 71.30; H, 8.79; N, 12.06.

[3H] 8-OH-DPAT Binding Studies

The binding of [3H] 8-OH-DPAT to rat hippocampal membrane was determined essentially as described by Peroutka [14]. Briefly, the hippocampus was excised from male Sprague-Dawley rats (250–280 g) and homogenized in 50 vol Tris-HCl buffer (50 mM, pH 7.4 at 37 °C). The homogenates were centrifuged (40,000 *g* for 10 min) and the pellets washed twice by centrifugation and resuspension with an intermediate incubation for 15 min at 37 °C to remove endogenous 5-HT. The final pellet was resuspended in 100 vol Tris-Buffer. Throughout the procedure the tissue was kept at 0–4 °C unless otherwise stated. Tissue homogenate (600 mg) was incubated for 50 min at 37 °C with [^{3}H] 8-OH-DPAT, 100 mM ascorbic acid and 10 mM pargyline in the presence and absence of displacing agent. The concentrations of test compounds which inhibited the specific binding by 50 % (IC_{50} values) were measured by using 1.5 nM [^{3}H] 8-OH-DPAT and 7 concentrations of the unlabelled compounds between 10^{-12} and 10^{-5} M. Nonspecific binding was defined as that determined in the presence of 10 mM 5-HT. IC_{50} values were determined from the competition binding data using computer-assisted curve fitting with GraphPad Prism 3.0 program. Inhibition binding constant (Ki) values were subsequently calculated from IC_{50} values using the Cheng-Prusoff equation [15].

References

[1] M. M. Rapport, A. A. Green, I. H. Page, *J. Biol. Chem.* **1948**, *176*, 1243–1251.

[2] S. J. Peroutka, *Trends Neurosci.* **1988**, *11*, 496–500.

[3] E. Zifa, G. Fillion, *Pharmacol. Rev.* **1992**, *44*, 401–458.

[4] M. E. Newman, B. Lerer, B. Shapiro, *Prog. Neuropsychopharmacol. Biol. Psychiatry* **1993**, *17*, 1–19.

[5] K. P. Lesch, *Prog. Neuropsychopharmacol. Biol. Psychiatry* **1991**, *15*, 723–733.

[6] S. E. File, *Pharmacol. Biochem. Behav.* **1996**, *54*, 3–12.

[7] H. G. Baumgartöen, M. Göthert, in *Serotonergic Neurons and 5-HT Receptors in the CNS*, Springer-Verlag, Berlin **1997**.

[8] B. Olivier, I. van Wijngaarden, W. Soudijn, in *Serotonin Receptors and their Ligands*, Elsevier, Amsterdam **1997**.

[9] J. De Vry, *Psychopharmacology* **1995**, *121*, 1–26.

[10] A. S. Eison, M. S. Eison, *Prog. Neuropsychopharmacol. Biol. Psychiatry* **1994**, *18*, 47–62.

[11] M. D. Hall, S. el Mestikawy, M. B. Emerit, L. Pichat, M. Hamon, H. Gozlan, *J. Neurochem.* **1985**, *44*, 1685–1696.

[12] M. Hamon, H. Gozlan, S. el Mestikawy, M. B. Emerit, F. Bolanos, L. Schechter, *Ann. N. Y. Acad. Sci.* **1990**, *600*, 114–129.

[13] J. M. Palacios, C. Waeber, D. Hoyer, G. Mengod, *Ann. N. Y. Acad. Sci.* **1990**, *600*, 36–52.

[14] S. J. Peroutka, *J. Neurochem.* **1986**, *47*, 529–540.

[15] Y. Cheng, W. H. Prusoff, *Biochem. Pharmacol.* **1973**, *22*, 3099–3108.