Synthesis of 4-Substituted 2-(4-Methylpiperazino)pyrimidines and Quinazoline Analogs as Serotonin 5-HT_{2A} Receptor Ligands

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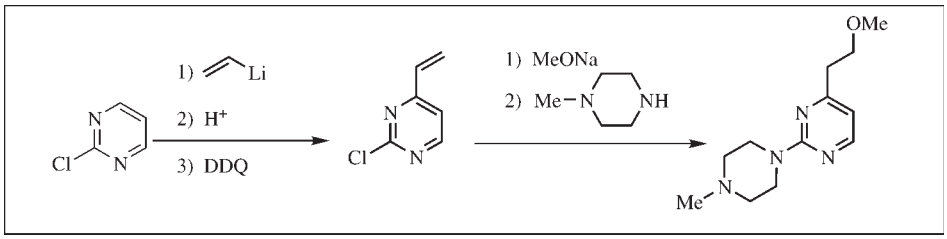

The addition reaction of lithium reagents to the 4 position of 2-chloropyrimidine or 2-chloroquinazoline followed by oxidation of the resultant dihydro intermediate product is a powerful tool for the synthesis of 4-substituted 2-chloropyrimidines or 2-chloroquinazolines. 4-Vinyl derivatives undergo a conjugate nucleophilic addition across the vinyl group. A nucleophilic displacement of chloride in 4-substituted 2-chloropyrimidines or 2-chloroquinazolines by treatment with 4-methylpiperazine provides compounds that are antagonists of the serotonin 5-HT_{2A} receptor.

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INTRODUCTION

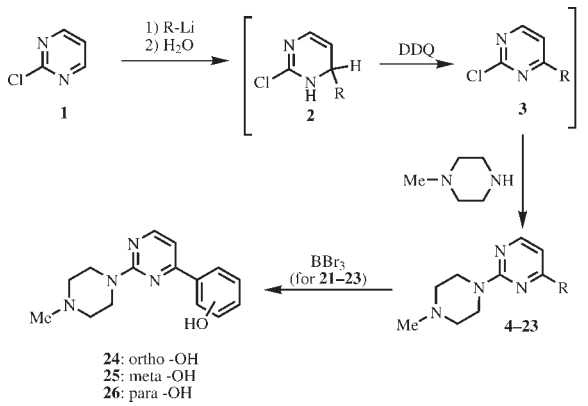
The addition reaction of organolithium reagents to the formal C=N bond in electron-deficient heteroaromatic compounds is known as the Ziegler reaction [3]. In particular, the addition reaction of organolithium reagents across the formal N3=C4 double bond in 2-chloropyrimidine followed by oxidation (aromatization) of the resultant adduct 2 (Scheme 1) is a powerful tool for the synthesis of 4-substituted 2-chloropyrimidines 3 [4,5]. The synthetic utility of this methodology is further enhanced by the facile nucleophilic displacement of chloride in 3 with common nucleophiles. In particular, 2-(4-methylpiperazino)pyrimidines obtained by this approach have been shown to interact with the central nervous system (CNS) (Chart 1) [6–9].

Related compounds bind with nucleic acids [10–15], enhance activity of the antitumor antibiotic bleomycin [16,17], and are anti-HIV-1 agents [18,19]. Surprisingly, relatively few potential CNS agents have been obtained, that is, only a limited number of simple 4-substituted pyrimidines have been synthesized by using this methodology. Herewith, we report that the synthetic sequence of Scheme 1 provides an easy access to pyrimidines containing structurally diverse groups at position 4. Because some of the previously reported 4-substituted 2-(4-methylpiperazino)pyrimidines are potent 5-HT_{2A} ligands (Chart 1, Table 1), the majority of new derivatives, obtained as part of this work, were tested for binding to the 5-HT_{2A} sites. This serotonin receptor is of immense interest because of its role in normal brain function. In particular, the powerful hallucinogens, such as LSD, presumably have the 5-HT_{2A} receptor as their primary target [20,21].

RESULTS AND DISCUSSION

The original synthetic route to 4-substituted 2-chloropyrimidines 3 (Scheme 1) was developed in our laboratories using a limited number of organolithium reagents R-Li [4,5]. The current study of the scope of this chemistry revealed that a large number of diverse compounds 3 can easily be synthesized. The 2-chloropyrimidines 3 are precursors to biologically active 2-aminopyrimidine derivatives [7–10]. As part of this work, it was found that the 2-aminopyrimidine derivatives, such as 4-23 in Scheme 1, can be prepared by using crude intermediate products 2 and 3. Thus, the methodology was greatly simplified. The yields of selected products 4–23 obtained using analytically pure and crude intermediate products 3 were similar. Purification of products 4–23 involved chromatography. Because most of these compounds are oils, they were transformed into hydrobromides, and the

Scheme 1



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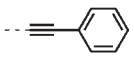
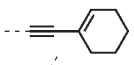
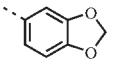
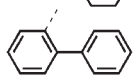
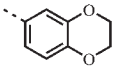
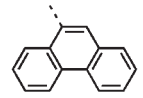
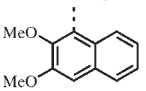
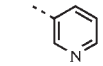
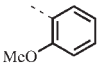
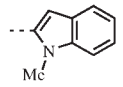
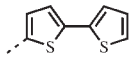
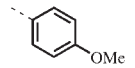
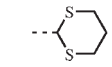
5	*sec*-Bu		
6	*tert*-Bu	16	
7		17	
8		18	
9		19	
10		20	
11		21	
12		22	
13		23	
14			

salts were additionally purified by crystallization. Conversely, demethylation of methoxyphenyl derivatives 21–23 by treatment with boron tribromide gave the corresponding hydrobromide salts 24–26 directly.

Chart 1

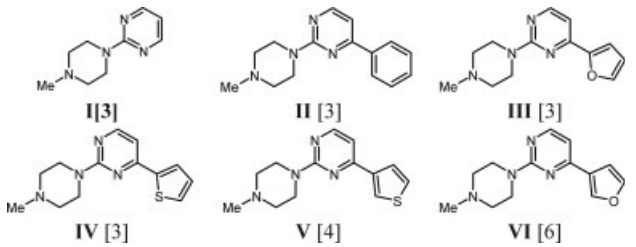


Table 1

5-HT_{2A} affinity data of compounds **I–VI**, **4–26**, **29**, **31**, **35** and **37**.

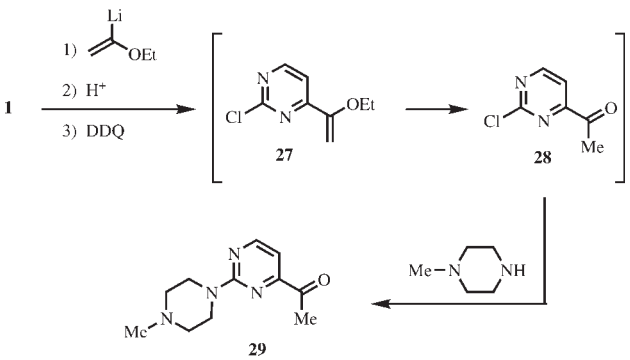
#	K_i 5-HT_{2A} [nM][a]	#	K_i 5-HT_{2A} [nM][a]
I[b]	19 700	**15**	5280
II[b]	2 095	**16**	>10 000
III[b]	745	**17**	2 142
IV[b]	208	**18**	3 815
V[c]	192	**19**	2 670
VI[d]	10	**20**	>10 000
4	410	**21**	1 209
5	254	**22**	544
6	206	**23**	875
7	3 427	**24**	1 936
8	1 142	**25**	>10 000
9	31	**26**	1 243
10	3 910	**29**	547
11	>10 000	**31**	656
12	854	**35**	388
13	>10 000	**37**	>10 000
14	5 257		

[a] The estimated K_i values (see ref. 24 for the protocol).
[b] Ref. 6.
[c] Ref. 7.
[d] Ref. 9.

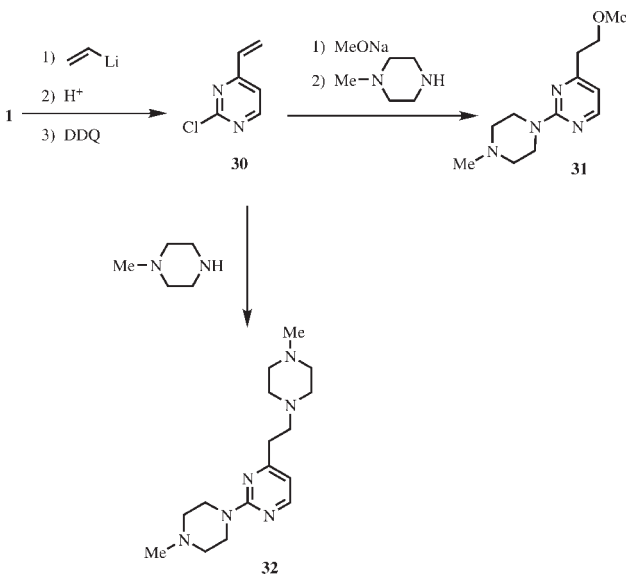
The introduction of the acetyl group at position 4 of the pyrimidine was achieved by using the umpolung approach [22]. Thus, a nucleophilic reagent derived from ethyl vinyl ether was allowed to react with 2-chloropyrimidine (1) followed by aromatization of the resultant adduct by treatment with 2,3-dichloro-5,6-dicyanoquinone (DDQ) to give the intermediate product 27 (Scheme 2). Then the ethoxyvinyl function in 27 was hydrolyzed under acidic conditions to give the acetyl-substituted pyrimidine 28. Nucleophilic displacement of chloride in 28 by treatment with *N*-methylpiperazine furnished the desired compound 29 in an overall yield of 70%. It should be noted that this preparation was achieved using crude intermediate products 27 and 28.

A vinyl function is easily introduced at position 4 of 2-chloropyrimidine (1, Scheme 3) or 2-chloroquinazoline (33, Scheme 4) by using the discussed chemistry.

Scheme 2



Scheme 3



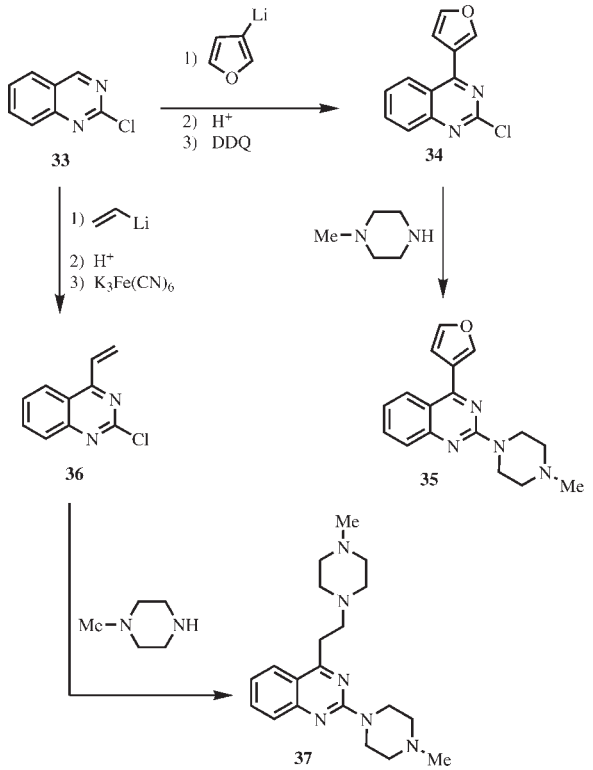
While 2-chloro-4-vinylpyrimidine (30) has been obtained previously using cumbersome chemistry [23], its quinazoline analog 36 is a new compound. In the synthesis of 36, the general protocol was modified in that the intermediate 2-chloro-4-vinyl-3,4-dihydroquinazoline (data not shown) was aromatized by the reaction with potassium ferricyanide, which has previously been used for the oxidation of 4-vinyl-3,4-dihydroquinazoline [24]. The standard treatment of the adduct with DDQ resulted in opening of the pyrimidine subunit, which was previously demonstrated [4]. The vinyl derivatives 30 and 36 are unusual substrates for the reaction with nucleophiles in that they undergo conjugate addition across the vinyl group. Thus, treatment of 30 with 1 equivalent of sodium methoxide and then with *N*-methylpiperazine furnished product 31 in an overall yield of 58%. This result shows that the methoxy anion undergoes selective conjugate addition reaction with the involvement of the vinyl group, and then chloride in the intermediate product (not shown) is displaced by the reaction with the amine. Conversely, the reaction of 30 with 1 equivalent of *N*-methylpiperazine gave a mixture of products that was difficult to separate, suggesting no selectivity between the conjugate addition and chloride displacement reactions. The treatment of 30 with excess amine gave the expected compound 32 as the sole product. In a similar way, the reaction of 2-chloro-4-vinylquinazoline (36, Scheme 4) with *N*-methylpiperazine furnished the displacement/addition product 37. It should be noted that the conjugate addition reactions with vinyl-substituted heterocyclic compounds are extremely rare, and we are aware of only single report on the conjugate addition to a vinylpyrimidine substrate [25].

In addition to the introduction of the vinyl group at position 4 of 2-chloroquinazoline as discussed earlier, a number of other 4-substituted quinazolines was synthesized using the discussed approach. This is illustrated in Scheme 4 by the preparation of 4-(3-furyl)-2-(4-methylpiperazino)quinazoline through the intermediary of 2-chloro analog 34. Again, the simplified methodology was used in that the intermediate product 34 was not purified before the treatment with the amine.

New compounds were evaluated for their affinity to serotonin 5-HT_{2A} receptors according to the previously validated and published procedure [26]. The results of binding experiments are summarized in Table 1. The majority of new 4-substituted 2-(4-methylpiperazino)-pyrimidines show greater 5-HT_{2A} affinity than the unsubstituted compound I. The highest affinity was found for biphenyl derivative 9, which is somewhat surprising, because the phenyl analog II displays only moderate activity (K_i = 2095 nM).

Because the 3-furyl derivative VI was earlier characterized as a potent 5-HT_{2A} ligand [10], compounds 15–26, 29 and 31 were designed to have an oxygen atom in the substituent of the pyrimidine. Unfortunately, all these compounds are less active than the previously reported ligand VI. Quinazoline ligand 35 is also less active than its pyrimidine analog VI.

Scheme 4



In conclusion it seems that the ligand binding pocket in 5-HT_{2A} receptor has very discriminating structural requirements. The finding of the highly active biphenyl derivative 9 suggests possible direction of further structural modifications of 2-(4-methylpiperazino)-pyrimidines.

EXPERIMENTAL

General. All organometallic reactions were conducted under a nitrogen atmosphere in tetrahydrofuran distilled from sodium benzophenone ketyl immediately before use. Final products were purified on a chromatotron using silica gel-coated rotors (2 mm). Hydrobromide or hydrochloride salts of the piperazine products were obtained by using a general procedure [7], and the salts were crystallized from 95% ethanol. In several cases, it was necessary to dilute the ethanolic solution with ether to induce crystallization. Melting points (Pyrex capillary) are not corrected. ^{1}H NMR spectra were recorded at 400 MHz. Unless stated otherwise, the spectra were obtained for free bases in deuteriochloroform.

Lithium reagents. *n*-Butyllithium (2.0*M* in cyclohexane), *sec*-butyllithium (1.4*M* in cyclohexane), and *tert*-butyllithium (1.7*M* in pentane) were commercial reagents. The following lithium reagents (required for the preparation of compounds given in parentheses) were generated by bromine-lithium exchange reaction: 2-lithiobiphenyl (**9**), 9-lithiophenanthrene (**10**), 3-lithiopyridine (**11**), 5-lithio-2,2′-bithiophene (**13**), 4-lithio-1,2-(methylenedioxy)benzene (**18**), 6-lithio-1,4-benzodioxane (**19**), 1-lithio-2,3-dimethoxynaphthalene (**20**), 2-lithioanisole (**21**), 3-lithioanisole (**22**), 4-lithioanisole (**23**), and 3-lithiofuran (**35**). Briefly, a solution of the corresponding bromo derivative (12.5 mmol) in anhydrous tetrahydrofuran (15 mL) was cooled to −70°C and treated dropwise with *n*-butyllithium (6.3 mL, 12.6 mmol) for 5 min. Then the mixture was kept at −70°C for 2 h before treatment with 2-chloropyrimidine. The following lithium reagents (required for the preparation of compounds given in parentheses) were generated by lithiation (hydrogen-lithium exchange): 1-lithio-2-phenylacetylene (**7**), 1-lithio-2-(cyclohexen-1-yl)acetylene (**8**), 6-lithio-3,4-dihydro-2*H*-pyran (**17**), and 1-lithio-1-ethoxyethylene (**29**). Briefly, a solution of the corresponding substrate (12.5 mmol) in anhydrous tetrahydrofuran (15 mL) was treated at −10°C with *tert*-butyllithium (7.4 mL, 12.6 mmol), and the mixture was allowed to stand at this temperature for 10 min before cooling to −70°C. To generate 2-lithio-1,3-dithiane (for the preparation of **14**), a mixture of 1,3-dithiane (12.5 mmol) and *n*-butyllithium (6.3 mL, 12.6 mmol) in anhydrous tetrahydrofuran (10 mL) was allowed to react at −25°C for 3 h before cooling to −70°C. 2-Lithio-1,3-dioxolane (for **15**) and 2-lithio-1,3-dioxane (for **16**) were generated from the corresponding stannyl derivatives, as reported in the literature [27,28]. This is a multistep synthesis, and the final step was adjusted to generate 12.5 mmol of the lithium reagent in 15 mL of tetrahydrofuran. Vinyllithium (for **31**, **32**, and **37**) was generated by the reaction of tetravinyltin with *tert*-butyllithium as previously described [28,29]. Briefly, a solution of tetravinyltin (0.7 mL, 3.2 mmol) in tetrahydrofuran (15 mL) was treated dropwise at −70°C for 5 min with *tert*-butyllithium (7.4 mL, 12.6 mmol), and the mixture was stirred for an additional 15 min at −70°C before use.

General procedure for the synthesis of 4-substituted 2-(4-methylpiperazino)pyrimidines 4–23. A solution of the corresponding lithium reagent (12.5 mmol) was treated dropwise at −70°C with a solution of 2-chloropyrimidine (1.35 g, 12 mmol) in tetrahydrofuran (15 mL). The mixture was stirred and allowed to reach gradually 0°C within 2 h, then quenched with a solution of water (1 mL) in tetrahydrofuran (5 mL). After treatment with a solution of DDQ (2.8 g, 12.5 mmol) in tetrahydrofuran (15 mL), the mixture was stirred at 23°C for 5 min, then cooled to 0°C, treated with a cold solution of sodium hydroxide (4*M*, 5 mL, 20 mmol), and extracted at 0°C with cold hexanes (20 mL). The residue was additionally extracted with a mixture of ether or hexanes (1:1, 2 × 15 mL), and the organic extracts were combined, dried over sodium sulfate, and passed through silica gel (5 g) to remove tar. Concentration on a rotary evaporator gave crude 4-substituted 2-chloropyrimidine **3** that, without further purification, was used for the reaction with *N*-methylpiperazine. Thus, a solution of crude compound **3** and *N*-methylpiperazine (5.5 mL, 50 mmol) in toluene (20 mL) was heated to 70°C until a thin layer chromatography analysis on silica gel eluting with ethyl acetate or triethylamine (95:5) showed the absence of **1** (several hours). Filtration of the mixture was followed by concentration on a rotary evaporator and chromatography of the residue eluting with ethyl acetate or triethylamine/hexanes (90:5:5). All products **4–23** were transformed into salts as mentioned earlier (see General Section). Selected intermediate products **3** (R = *n*-Bu, 9-phenanthryl, 2,2′-bithiophen-5-yl) were purified by chromatography as described earlier before the treatment with *N*-methylpiperazine. The yields of the corresponding products **4**, **10**, and **13** and the yields of the same respective products obtained using crude compounds **3** were similar (±1%).

4-Butyl-2-(4-methylpiperazino)pyrimidine (4). This compound was obtained as an oil in 68% yield; ^{1}H NMR: δ 0.94 (t, *J* = 7 Hz, 3H), 1.38 (m, 2H), 1.67 (m, 2H), 2.34 (s, 3H), 2.47 (m, 4H), 2.56 (t, *J* = 7 Hz, 2H), 3.85 (m, 4H), 6.37 (d, *J* = 5 Hz, 1H), 8.18 ppm (d, *J* = 5 Hz, 1H). The hydrobromide salt had mp 100–101°C. Anal. Calcd. for $2C_{13}H_{22}N_4 \cdot 4HBr \cdot H_2O$: C, 38.53; H, 6.22; N, 13.83. Found: C, 38.34; H, 6.23; N, 13.77.

4-(sec-Butyl)-2-(4-methylpiperazino)pyrimidine (5). This compound was obtained as an oil in 42% yield; ^{1}H NMR: δ 0.84–0.88 (m, 3H), 1.20–1.22 (m, 3H), 1.63 (m, 2H), 2.34 (s, 3H), 2.47 (m, 4H), 2.53 (m, 1H), 3.85 (m, 4H), 6.35 (d, *J* = 5 Hz, 1H), 8.19 ppm (d, *J* = 5 Hz, 1H). The hydrobromide salt had mp 177–178°C. Anal. Calcd. for $C_{13}H_{22}N_4 \cdot HBr$: C, 49.53; H, 7.35; N, 17.77. Found: C, 49.41; H, 7.47; N, 17.47.

4-(tert-Butyl)-2-(4-methylpiperazino)pyrimidine (6). This compound was obtained as an oil in 53% yield; ^{1}H NMR: δ 1.27 (s, 9H), 2.47 (m, 4H), 3.85 (m, 4H), 6.51 (d, *J* = 5 Hz, 1H), 8.21 ppm (d, *J* = 5 Hz, 1H). The hydrobromide salt had mp 224–226°C. Anal. Calcd. for $4C_{13}H_{22}N_4 \cdot 4HBr \cdot H_2O$: C, 48.15; H, 7.46; N, 17.28. Found: C, 47.82; H, 7.16; N, 16.93.

2-(4-Methylpiperazino)-4-(phenylethynyl)pyrimidine (7). This compound was obtained as an oil in 60% yield; ^{1}H NMR: δ 2.24 (s, 3H), 2.48 (t, *J* = 5 Hz, 4H), 3.89 (t, *J* = 5 Hz, 4H), 6.68 (d, *J* = 5 Hz, 1H), 7.39 (m, 3H), 7.61 (m, 2H), 8.30 ppm (d, *J* = 5 Hz, 1H). The hydrobromide salt had mp 193–195°C. Anal. Calcd. for $C_{17}H_{18}N_4 \cdot 2HBr \cdot H_2O$: C, 44.56; H, 4.84; N, 12.23. Found: C, 44.18; H, 4.82; N, 11.94.

4-[(Cyclohexen-1-yl)ethynyl)]-2-(4-methylpiperazino)- pyrimidine (8). This compound was obtained as an oil in 59% yield; ^{1}H NMR: δ 1.66 (???m, 4H), 2.20 (m, 4H), 2.34 (s, 3H), 2.46 (m,4H), 3.85 (m, 4H), 6.37 (m, 1H), 6.55 (d, J = 5 Hz, 1H), 8.24 ppm (d, J = 5 Hz, 1H). The hydrobromide salt had mp 242°C (decomp). Anal. Calcd. for $C_{17}H_{22}N_4$·HBr: C, 56.20; H, 6.38; N, 15.42. Found: C, 56.08; H, 6.47; N, 15.34.

2-(4-Methylpiperazino)-4-(2-biphenyl)pyrimidine (9). This compound had mp 8587°C and was obtained in 86% yield; ^{1}H NMR: δ 2.04 (s, 3H), 2.37 (m, 4H), 3.67–3.69 (m, 4H), 6.29 (d, J = 5 Hz, 1H), 7.25 (m, 3H), 7.44 (m, 3H), 7.70 (m, 3H), 8.09 ppm (d, J = 5 Hz, 1H). Anal. Calcd. for $C_{21}H_{22}N_4$·2HBr·H_2O: C, 49.43; H, 5.14; N, 10.98. Found: C, 49.32; H, 5.00; N, 10.57.

2-(4-Methylpiperazino)-4-(9-phenanthryl)pyrimidine (10). This compound was obtained as an oil in 78% yield; ^{1}H NMR: δ 2.32 (s, 3H), 2.48 (m, 4H), 3.93–3.97 (m, 4H), 6.81 (d, J = 5 Hz, 1H), 7.58 (m, 2H), 7.63–7.67 (m, 2H), 7.89 (m, 2H), 8.28 (d, J = 8 Hz, 1H), 8.44 (d, J = 5 Hz, 1H), 8.70 ppm (m, 2H). The hydrobromide salt had mp 195–198°C. Anal. Calcd. for $2C_{23}H_{22}N_4$·3HBr·$4H_2O$: C, 53.97; H, 5.42; N, 10.95. Found: C, 54.35; H, 5.04; N, 10.96.

2-(4-Methylpiperazino)-4-(3-pyridyl)pyrimidine (11). This compound was obtained as an oil in 84% yield. The hydrobromide salt had mp 163–165°C; ^{1}H NMR (salt, deuterated dimethyl sulfoxide): δ 2.87(s, 3H), 3.13 (m, 2H), 3.37 (m, 2H), 3.55 (m, 2H), 4.91 (m, 2H), 7.55 (d, J = 5 Hz, 1H), 7.91 (m, 1H), 8.66 (d, J = 5 Hz, 1H), 8.92 (m, 2H), 9.53 (s, 1H), 9.93 ppm (br s, 2H).Anal. Calcd. for $22C_{14}H_{17}N_5$·4HBr·$3H_2O$: C, 37.86; H, 4.99; N, 15.77. Found: C, 38.02; H, 4.66; N, 15.58.

4-(1-Methylindol-2-yl)-2-(4-methylpiperazino)pyrimidine (12). This compound was obtained as an oil in 78%; ^{1}H NMR: δ 240 (s, 3H), 2.55 (m, 4H), 3.94 (m, 4H), 4.18 (s, 3H), 6.97 (d, J = 5 Hz, 1H), 7.06 (s, 3H), 7.19 (t, J = 8 Hz, 1H), 7.36 (t, J = 8 Hz, 1H), 7.45 (d, J = 8 Hz, 1H), 7.70 (d, J = 8 Hz, 1H), 8.38 ppm (d, J = 5 Hz, 1H). The hydrobromide salt had mp 302–303°C. Anal. Calcd. for $2C_{18}H_{23}N_5$·4HBr·H_2O: C, 45.02; H, 5.46; N, 14.58. Found: C, 45.10; H, 5.26; N, 14.47.

4-(2,2′-Bithiophen-5-yl)-2-(4-methylpiperazino)-pyrimidine (13). This compound was obtained as an oil in 76% yield; ^{1}H NMR: δ 2.36 (s, 3H), 2.50 (m, 4H), 3.92 (m, 4H), 6.79 (d, J = 5 Hz, 1H), 7.05 (t, J = 4 Hz, 1H), 7.18 (d, J = 4 Hz, 1H), 7.27 (m, 2H), 7.55 (d, J = 4 Hz, 1H), 8.29 ppm (d, J = 5 Hz, 1H). The hydrobromide salt had mp 187–190°C. Anal. Calcd. for $2C_{17}H_{18}N_4S_2$·3HBr·$4H_2O$: C, 40.85; H, 4.74; N, 11.21. Found: C, 40.54; H, 4.41; N, 11.04.

4-(1,3-Dithiane-2-yl)-2-(4-methylpiperazino)pyrimidine (14). This compound was obtained as an oil in 69% yield; ^{1}H NMR: δ 204 (m, 2H), 2.17 (m, 1H), 2.35 (s, 3H), 2.47 (m, 4H), 3.03 (m, 4H), 3.88 (m, 4H), 8.30 (d, J = 5 Hz, 1H), 8.65 ppm (d, J = 5 Hz, 1H). The hydrobromide salt had mp 175–176°C. Anal. Calcd. for $C_{13}H_{20}N_4S_2$·2HBr: C, 34.07; H, 4.84; N, 12.23. Found: C, 34.30; H, 5.13; N, 12.02.

4-(1,3-Dioxolane-2-yl)-2-(4-methylpiperazino)pyrimidine (15). This compound was obtained as an oil in 69% yield; ^{1}H NMR: δ 233 (s, 3H), 2.46 (t, J = 5 Hz, 4H), 3.87 (t, J = 5 Hz, 4H), 4.10 (m, 4H), 5.60 (s, 1H), 6.66 (d, J = 5 Hz, 1H), 8.34 ppm (d, J = 5 Hz, 1H). The hydrobromide had mp 166–170°C. Anal. Calcd. for $C_{12}H_{18}N_4O_2$·HBr: C, 43.53; H, 5.78; N, 16.92. Found: C, 43.87; H, 5.87; N, 17.00.

4-(1,3-Dioxane-2-yl)-2-(4-methylpiperazino)pyrimidine (16). This compound was obtained as an oil in 71% yield The hydrobromide salt had mp 179–180°C; ^{1}H NMR (salt, deuteriochloroform): δ 1.49 (m, 1H),2.26(m, 1H), 2.82 (s, 3H), 2.85 (m, 2H), 3.59 (m, 2H), 3.94 (m, 4H), 4.28 (m, 2H), 4.98 (m, 2H), 5.32 (s, 1H), 6.97 (d, J = 5 Hz, 1H), 8.42 ppm (d, J = 5 Hz, 1H). Anal. Calcd. for $2C_{13}H_{20}N_4O_2$·2HBr·H_2O: C, 44.08; H, 6.26; N, 15.82. Found: C, 43.93; H, 6.01; N, 15.64.

4-(3,4-Dihydro-2H-pyran-6-yl)-2-(4-methylpiperazino)-pyrimidine (17). This compound was obtained as an oil in 80% yield; ^{1}H NMR: δ 1.91 (m, 2H), 2.25 (m, 2H), 2.33 (s, 3H), 2.47 (m, 4H), 3.86 (m, 4H), 4.15 (m, 2H), 6.21 (m, 1H), 6.74 (d, J = 5 Hz, 1H), 8.32 ppm (d, J = 5 Hz, 1H). The hydrobromide had mp 192–194°C. Anal. Calcd. for $4C_{14}H_{20}N_4O$·5HBr·$2H_2O$: C, 45.39; H, 6.05; N, 15.12. Found: C, 45.71; H, 6.08; N, 15.27.

4-(3,4-Methylenedioxyphenyl)-2-(4-methylpiperazino)-pyrimidine (18). This compound was obtained in 77% yield; mp (free base) 115–116°C; mp (hydrobromide salt) 287–288°C; ^{1}H NMR: δ 2.39 (s, 3H), 2.57 (m, 4H), 3.96 (m, 4H), 6.06 (s, 2H), 6.88 (d, J = 5 Hz, 1H), 6.92 (d, J = 8 Hz, 1H), 7.61 (m, 2H), 8.36 ppm (d, J = 5 Hz, 1H). Anal. Calcd. for $C_{16}H_{18}N_4O_2$·2HBr: C, 41.76; H, 4.38; N, 12.18. Found: C, 41.58; H, 4.43; N, 12.12.

4-(1,4-Benzodioxane-4-yl)-2-(4-methylpiperazino)-pyrimidine (19). This compound was obtained as an oil in 81% yield; ^{1}H NMR: δ 2.38 (s, 3H), 2.57 (m, 4H), 3.96 (m, 4H), 4.33 (s, 4H), 6.89 (d, J = 5 Hz, 1H), 6.97 (d, J = 8 Hz, 1H), 7.57 (m, 1H), 7.68 (m, 1H), 8.35 ppm (d, J = 5 Hz, 1H). The hydrobromide salt had mp 297–298°C. Anal. Calcd. for $2C_{17}H_{20}N_4O_2$·4HBr·H_2O: C, 42.26; H, 4.80; N, 11.60. Found: C, 42.29; H, 4.65; N, 11.55.

4-(2,3-Dimethoxy-1-naphthyl)-2-(4-methylpiperazino)-pyrimidine (20). This compound was obtained as an oil in 70% yield; ^{1}H NMR: δ 2.37 (s, 3H), 2.51 (m, 4H), 3.85 (s, 3H), 3.93 (m, 4H), 4.05 (s, 3H), 6.69 (d, J = 5 Hz, 1H), 7.27 (s, 1H), 7.32 (m, 1H), 7.42 (m, 1H), 7.59 (d, J = 8 Hz, 1H), 7.78 (d, J = 8 Hz, 1H), 8.47 ppm (d, J = 5 Hz, 1H). The hydrobromide salt had mp 240–241°C. Anal. Calcd. for $4C_{21}H_{23}N_4O_2$·4HBr·H_2O: C, 56.19; H, 5.50; N, 12.48. Found: C, 56.01; H, 5.68; N, 12.48.

4-(2-Methoxyphenyl)-2-(4-methylpiperazino)pyrimidine (21). This compound was obtained in 88% yield; mp (free base) 79–80°C; mp (hydrobromide salt) 191–192°C; ^{1}H NMR: δ 238 (s, 3H), 3.51 (m, 4H), 3.91 (s, 3H), 3.93 (m, 4H), 7.03 (d, J = 8Hz, 1H), 7.18 (t, J = 8 Hz, 1H), 7.21 (d, J = 5 Hz, 1H), 7.43 (m, 1H), 8.01 (d, J = 8 Hz, 1H), 8.36 ppm (d, J = 5 Hz, 1H). Anal. Calcd. for $2C_{16}H_{20}N_4O$·4HBr·H_2O: C, 42.22; H, 5.09; N, 12.31. Found: C, 42.25; H, 5.06; N, 12.33.

4-(3-Methoxyphenyl)-2-(4-methylpiperazino)pyrimidine (22). This compound was obtained as an oil in 80% yield; ^{1}H NMR: δ 237 (s, 3H), 2.57 (m, 4H), 3.90 (s, 3H), 3.97 (m, 4H), 6.95 (d, J = 5 Hz, 1H), 7.42 (t, J = 8 Hz, 1H), 7.63 (m, 3H), 8.39 ppm (d, J = 5 Hz, 1H). The hydrobromide had mp 244–245°C. Anal. Calcd. for $2C_{16}H_{20}N_4O$·4HBr·H_2O: C, 42.20; H, 5.09; N, 12.31. Found: C, 42.18; H, 5.08; N, 12.35.

4-(4-Methoxyphenyl)-2-(4-methylpiperazino)pyrimidine (23). This compound was obtained in 89% yield; mp (free base) 66–67°C; mp (hydrobromide salt) 278–279°C; ^{1}H NMR: δ 237 (s, 3H), 2.52 (m, 4H), 3.89 (s, 3H), 3.96 (m, 4H), 6.90 (d, J = 5 Hz, 1H), 6.98 (m, 2H), 8.04 (m, 2H), 8.34 ppm (d, J = 5

Hz, 1H). Anal. Calcd. for $C_{16}H_{20}N_4O{\cdot}2HBr{\cdot}H_2O$: C, 41.40; H, 5.21; N, 12.07. Found: C, 41.74; H, 5.15; N, 12.03.

General procedure for demethylation of 21–23 to 24–26. A solution of **21–23** (free bases, 0.29 g, 1 mmol) in dichloromethane (10 mL) was treated at 23°C with boron tribromide in dichloromethane (1*M*, 4 mL, 4 mmol). The mixture was stirred at 23°C for 12 h and then quenched with a saturated solution of sodium bisulfate (5 mL). The resultant precipitate of the hydrobromide salt of **24–26** was filtered and crystallized from ethyl acetate or ether.

4-(2-Hydroxyphenyl)-2-(4-methylpiperazino)pyrimidine dihydrobromide (24·2HBr). This salt was obtained in 56% yield; mp 284–285°C; ^{1}H NMR (deuteriochloroform): δ 2.39(s, 3H), 2.55 (m, 4H), 3.86 (m, 4H), 6.97 (t, J = 8 Hz, 1H), 7.03 (d, J = 8 Hz, 1H), 7.06 (d, J = 5 Hz, 1H), 7.41 (t, J = 8 Hz, 1H), 7.79 (d, J = 8 Hz, 1H), 8.46 ppm (d, J = 5 Hz, 1H). Anal. Calcd. for $4C_{15}H_{18}N_4O{\cdot}8HBr{\cdot}H_2O$: C, 41.26; H, 4.73; N, 12.83. Found: C, 41.07; H, 4.61; N, 12.61.

4-(3-Hydroxyphenyl)-2(4-methylpiperazino)pyrimidine dihydrobromide (25·2HBr). This salt was obtained in 60% yield; mp >300°C; ^{1}H NMR (deuterated dimethyl sulfoxide): δ 3.21 (s, 3H), 3.56 (m, 4H), 4.76 (m, 4H), 6.96 (d, J = 5 Hz, 1H), 7.32 (t, J = 8 Hz, 1H), 7.63 (m, 3H), 8.51 ppm (d, J = 5 Hz, 1H). Anal. Calcd. for $4C_{15}H_{18}N_4O{\cdot}8HBr{\cdot}H_2O$: C, 41.26; H, 4.73; N, 12.83. Found: C, 41.11; H, 4.67; N, 12.70.

4-(4-Hydroxyphenyl)-2(4-methylpiperazino)pyrimidine dihydrobromide (26·2HBr). This salt was obtained in 60% yield; mp >300°C; ^{1}H NMR (deuterated dimethyl sulfoxide): δ 3.21 (s, 3H), 3.58 (m, 4H), 4.76 (m, 4H), 6.92 (d, J = 8 Hz, 2H), 7.32 (d, J = 5 Hz, 1H), 8.11 (d, J = 8 Hz, 2H), 8.45 ppm (d, J = 5 Hz, 1H). Anal. Calcd. for $2C_{15}H_{18}N_4O{\cdot}4HBr{\cdot}H_2O$: C, 40.84; H, 4.78; N, 12.70. Found: C, 40.84; H, 4.63; N, 12.58.

4-Acetyl-2-(4-methylpiperazino)pyrimidine (29). The reaction of 1-ethoxyvinyllithium (12.5 mmol) with 2-chloro-pyrimidine (1.35 g, 12 mmol) followed by aromatization of the resultant dihydropyrimidine intermediate by treatment with DDQ to give **27** was conducted as described earlier for other addition reactions. Crude product **27** was hydrolyzed to 4-acetyl-2-chloropyrimidine (**28**) by stirring the mixture of **27**, ethanol (25 mL), and hydrochloric acid (35%, 5 mL) at 23°C for 12 h. The acidic mixture was neutralized by addition of a saturated solution of sodium carbonate and then extracted with ether or hexanes (2:1, 3 × 50 mL). The extract was decolorized on a short column packed with silica gel (5 g), dried over magnesium sulfate and concentrated on a rotary evaporator. Crude product **28** gave the following ^{1}H NMR spectrum (deuteriochloroform): δ 2.27 (s, 3H), 7.84 (d, J = 5 Hz, 1H), 8.86 ppm (d, J = 5 Hz, 1H). Crude compound **28** was subjected to the reaction with *N*-methylpiperazine, and product **29** was purified by using the general procedure described earlier. Compound **29** (yield 70%) is an oil; ^{1}H NMR: δ 2.36 (s, 3H), 2.49 (m, 4H), 2.62 (s, 3H), 3.90 (m, 4H), 7.03 (d, J = 5 Hz, 1H), 8.50 ppm (d, J = 5 Hz, 1H). On heating, the hydrobromide salt **29**·1.5HBr undergoes melting with decomposition at 234°C. Anal. Calcd. for $2C_{11}H_{16}N_4O{\cdot}3HBr$: C, 38.67; H, 5.16; N, 16.40. Found: C, 38.82; H, 5.05; N, 16.41.

2-Chloro-4-vinylpyrimidine (30). The addition reaction of vinyllithium (25 mmol) with 2-chloropyrimidine (**1**, 24 mmol) followed by oxidation of the intermediate dihydropyrimidine was conducted by using a general procedure described earlier. After purification on a chromatotron eluting with hexanes or dichloromethane (2:1), compound **30** was obtained as an oil in 46% yield (1.5 g). The ^{1}H NMR spectrum of **30** [deuteriochloroform, δ 5.80 (m, 1H), 6.52 (m, 1H), 6.70 (m, 1H), 7.22 (d, J = 5 Hz, 1H), 8.57 ppm (d, J = 5 Hz, 1H)] was virtually identical with that reported in the literature for the compound obtained by an independent route [23].

4-(2-Methoxyethyl)-2-(4-methylpiperazino)pyrimidine (31). A solution of compound **30** (91 mg, 0.64 mmol) in anhydrous methanol (2 mL) was treated with a solution of sodium methoxide (0.5*M* in methanol, 0.65 mL, 0.65 mmol). The mixture was stirred at 23°C for 12 h, quenched with a saturated solution of sodium chloride (1 mL), and extracted with toluene (3 × 3 mL). The extract containing 2-chloro-4-(2-methoxyethyl)-pyrimidine was concentrated on a rotary evaporator to 3 mL and treated with *N*-methylpiperazine (0.25 mL, 2.0 mmol). The mixture was heated under reflux for 3 h, cooled, treated with a saturated solution of sodium carbonate (1 mL), and extracted with ether (2 × 5 mL), and the extract was concentrated on a rotary evaporator. Chromatography of the residue eluting with hexanes or triethylamine or methanol (4:1:1) gave 88 mg (58%) of **31** as an oil; ^{1}H NMR: δ 2.36 (s, 3H), 2.48 (m, 4H), 2.85 (t, J = 7 Hz, 2H), 3.37 (s, 3H), 3.77 (t, J = 7 Hz, 2H), 3.87 (m, 4H), 6.44 (d, J = 5 Hz, 1H), 8.22 ppm (d, J = 5 Hz, 1H). Anal. Calcd. for $C_{12}H_{21}N_4O{\cdot}HBr$: C, 30.09; H, 4.84; N, 11.70. Found: C, 29.86; H, 4.64; N, 12.02.

2-(4-Methylpiperazino)-4-[2-(4-methylpiperazino)ethyl]-pyrimidine (32). A mixture of 30 (0.33 g, 2.3 mmol) and *N*-methylpiperazine (0.55 mL, 5 mmol), and toluene (6 mL) was heated under reflux for 3 h. Workup and chromatography, as described for **31**, furnished 0.16 g (22%) of product **32** as an oil; ^{1}H NMR: δ 1.92 (m, 2H), 2.89 (s, 3H), 2.33 (s, 3H), 2.47 (m, 10H), 2.75 (m, 4H), 3.84 (m, 4H), 6.39 (d, J = 5 Hz, 1H), 8.17 ppm (d, J = 5 Hz, 1H). The hydrochloride has mp 202–206°C. Anal. Calcd. for $2C_{16}H_{28}N_4O{\cdot}8HCl{\cdot}H_2O$: C, 41.84; H, 7.24; N, 18.30. Found: C, 41.76; H, 7.10; N, 18.06.

4-(3-Furyl)-2-(4-methylpiperazino)quinazoline (35). The reaction of 2-chloroquinazoline [30] (**33**, 2.0 g, 12 mmol) with 3-furyllithium (12.5 mmol) and aromatization of the intermediate dihydroquinazoline by treatment with DDQ was conducted by using the general procedure described earlier. A mixture of the resultant crude product **34**, *N*-methylpiperazine 3 mL, 3 mmol, and toluene 15 mL was heated under reflux for 3 h, and the final product **35** was isolated and purified as described earlier. Product **35** was obtained in 18% yield (0.6 g); mp 67–69°C; ^{1}H NMR: δ 2.38 (s, 3H), 2.55(m, 4H), 4.05 (m, 4H), 7.02 (s, 1H), 7.22 (m, 1H), 7.60 (m, 1H), 7.66 (m, 2H), 8.08 ppm (m, 2H). Anal. Calcd. for $C_{17}H_{18}N_4O$: C, 69.37; H, 6.16; N, 19.03. Found: C, 69.21; H, 6.16; N, 18.83.

2-Chloro-4-vinylquinazoline (36). 2-Chloroquinazoline [30] (2.75 g, 12 mmol) in tetrahydrofuran (30 mL) was allowed to react with vinyllithium (12.5 mmol), and then the mixture was quenched by using the general procedure described earlier. A mixture of crude 2-chloro-4-vinyl-3,4-dihydroquinazoline thus obtained, potassium hydroxide (40 mg, 0.7 mmol), potassium ferricyanide (0.18 g, 0.55 mmol), water (0.3 mL), and benzene (1.5 mL) were stirred at 23°C for 5 h, and then treated with benzene (15 ml) and water (15 ml). The benzene layer was dried over magnesium sulfate, concentrated on a rotary evaporator, and the solid residue was crystallized from hexanes to give 29 mg (68%) of compound **36**; mp 65–67°C; ^{1}H NMR: δ 6.02 (m, 1H), 6.97 (m, 1H), 7.55 (m, 1H), 7.68 (m, 1H), 7.94

(m, 1H), 8.01 (m, 1H), 8.21 ppm (m, 1H). High resolution ms (esi, positive ion mode): Calcd. for $C_{10}H_7ClN_2$, *m*/*z* 190.0379 ($M^+ + 1$), found *m*/*z* 190.0376.

4-[2-(4-Methylpiperazino)ethyl]-2-(4-methylpiperazino)-quinazoline (37). A mixture of 36 (25 mg, 0.15 mmol), *N*-methylpiperazine (0.05 mL, 0.45 mmol), and toluene (2 mL) was heated to 70°C for 3 h. After cooling, the mixture was treated with a saturated solution of sodium carbonate (0.5 mL), extracted with ether (3 × 10 mL), and the extract was dried over magnesium sulfate and concentrated to give a solid residue. Chromatography eluting with hexanes or triethylamine or methanol (4:1:1, 100 mL; then 1:1:1, 400 mL) followed by crystallization from hexanes gave compound 37 in 40% yield (21 mg); mp 72–74°C; ^{1}H NMR: δ 2.33 (s, 3H), 2.37 (s, 3H), 2.52 (m, 8H), 2.66 (m, 4H), 2.96 (m, 2H), 3.35 (m, 2H), 4.00 (m, 4H), 7.20 (m, 1H), 7.60 (m, 2H), 7.88 ppm (d, $J = 8$ Hz, 1H). Anal. Calcd. for $C_{20}H_{30}N_6$: C, 67.76; H, 8.53; N, 23.71. Found: C, 67.93; H, 8.84; N, 23.96.

Radioligand Binding Studies. The *in vitro* affinity for native serotonin 5-HT_{2A} receptors was determined by inhibiting [^{3}H]-ketanserin (88 Ci/mmol; NEN Chemicals) binding to rat cortical membranes. Membrane preparation and a general assay procedure were carried out according to the previously published protocols [31]. Two compound concentrations were tested: 0.1 and 1 μ*M*, each run in triplicate. The Cheng and Prusoff equation was used for calculations of estimated K_i values [32].

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