Regioselective synthesis of new pyrimidine derivatives using organolithium reagents

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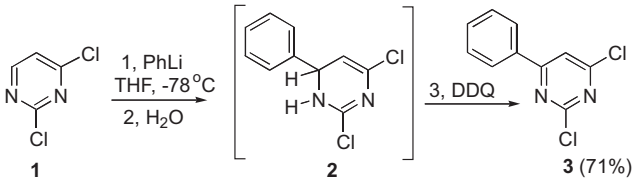
2,4-Dichloro-6-phenylpyrimidine (**3**) and 2-chloro-4-(1',3'-dithian-2'-yl)pyrimidine (**7**) were prepared using organolithium reagents. Nucleophilic attack on pyrimidines **1**, **3** and **9** using *N*-methylpiperazine was shown to be highly regioselective, favouring the formation of C-4 substituted products. Reaction of **7** with *N,N*-dimethylethylenediamine afforded **8** exclusively.

Keywords: pyrimidines, organolithium, regioselectivity, nucleophilic substitution

Pyrimidines are common heterocyclic compounds found in many natural products as well as synthetic drugs with antibacterial, and antimicrobial activities.[1] There is interest in the synthesis of 4,6-disubstituted pyrimidines.[2] Pyrimidines containing halogens at the 2- and 4-positions are excellent starting materials for introducing different aryl, alkyl or heteroaryl groups into the pyrimidine ring.[3,4] The highly electron-deficient character of the pyrimidine ring makes the nucleophilic aromatic substitution (S_NAr) reaction a general approach to the synthesis of a wide variety of pyrimidine derivatives, especially starting from the readily available halopyrimidines.[5] Here I report the introduction of a new hydrophobic side chain using organolithium reagents and the reactivity of the C-4 position of the halopyrimidines is generally found to be strongly preferred over C-2.

Since an increase in hydrophobic character of the substituents in the 4-position of the pyrimidine ring is expected to enhance the binding affinity with the serotonin (5-HT) receptor sites,[1,2] introduction of the hydrophobic groups phenyl, 1,3-dithianyl or naphthyl, as well as a cationic side chain, are expected to enhance affinity. The interaction of the ligand with an anionic side chain of the (5-HT) receptor site (Asp^{155}) neutralises the positive charge on the ligand bound to the receptor.

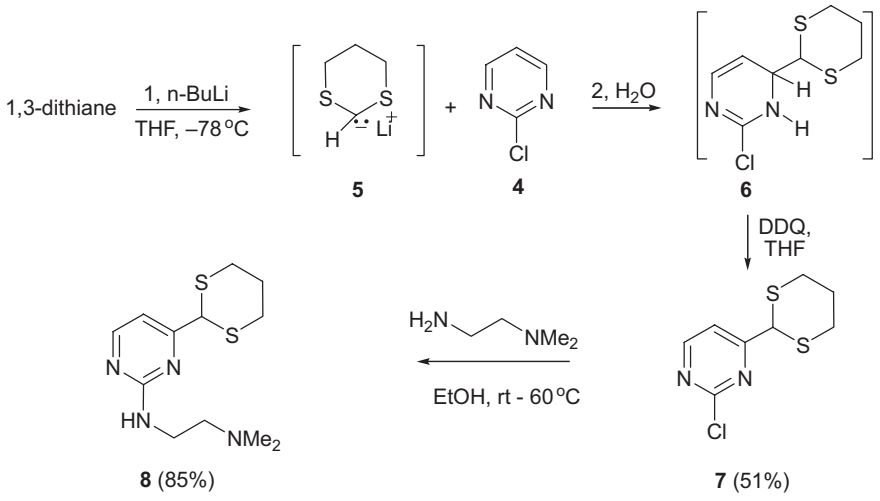
In order to extend the relationship between substituted pyrimidines and their biological activity, pyrimidines **3** and **7** were synthesised using organolithium reagents.[6-9] Nucleophilic addition to pyrimidine itself goes by regioselective addition to the N1-C6 azomethine bond. For example, phenyllithium undergoes nucleophilic addition to 2,4-chloropyrimidine (**1**)



Scheme 1

in preference to the N1–C6 bond rather than to the N1–C2 bond. Nucleophilic addition-elimination to the azomethine substituted by halogen takes place if all azomethine bonds are halogen substituted. In the present case, the reaction mixture is quenched with 1.5 molar equivalent of water to produce the dihydropyrimidine **2.** The dihydro adduct, without isolation, is treated with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in anhydrous tetrahydrofuran (THF) to form **3**. In this reaction, the substitution of hydrogen in the electron-deficient pyrimidine ring system by the action of nucleophilic agents can be considered as a hydride ion replacement. This reaction occurs via a two-step mechanism involving addition and elimination promoted by DDQ as an oxidising agent to give 2,4-dichloro-6-phenylpyrimidine (**3**) in 71% yield (Scheme 1).

The introduction of 1,3-dithiane at the 4-position of 2-chloropyrimidine (**4**) was brought about using 2-lithio-1,3-dithiane (**5**). This was generated by the action of n-butyllithium on 1,3-dithiane at –70°C, and then allowed to react with 2-chloropyrimidine (**4**) to produce the dihydro



Scheme 2

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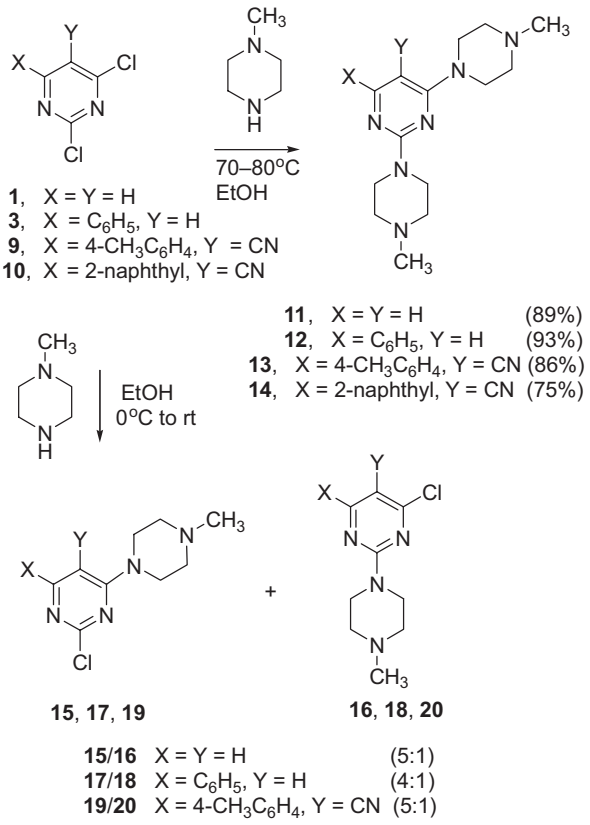

Scheme 3

intermediate (**6**). DDQ subsequently oxidised **6**, yielding 2-chloro-4-(1',3'-dithian-2'-yl)pyrimidine (**7**) in 51% yield. Compound **7** reacted with *N,N*-dimethylethylenediamine to give 2-[(*N,N*-dimethylaminoethyl)amino]-4-(1',3'-dithian-2'-yl) pyrimidine (**8**) in 85% yield (Scheme 2).

Pyrimidine derivatives with cationic side chains are known to be receptor binders with high selectivity.[1,2,6] Chloropyrimidines undergo direct nucleophilic chlorine substitution by common nucleophiles such as amines, hydroxide ion, mercaptides and alkoxides, as a rule regioselectively.[3-5] In the preparation of **11**–**14**, 2,4-dichloropyrimidines (**1**, **3**, **9** and **10**) were allowed to react with *N*-methylpiperazine in ethanol at 70–80°C to give 2,4-bis-(4'-methylpiperazin-1'-yl)pyrimidine (**11**), the corresponding 6-phenyl analogue (**12**), 2,4-bis-(4'-methylpiperazin-1'-yl)-6-(*p*-tolyl)pyrimidine-5-carbonitrile (**13**) and 2,4-bis-(4'-methylpiperazin-1'-yl)-6-(β-naphthyl)pyrimidine-5-carbonitrile (**14**) in 89%, 93%, 86% and 75% yields, respectively (Scheme 3). When the reactions between 2,4-dichloropyrimidines **1**, **3** and **9** and *N*-methylpiperazine were carried out at lower temperature (0°C to r.t), isomeric pairs of products **15**/**16** (5 : 1, 85%), **17**/**18** (4 : 1, 89%) and **19**/**20** (5 : 1, 87%) (relative ratios and combined yields as indicated), respectively. The isomeric pairs were separated by silica gel column chromatography using ether : hexanes : ethanol (2 : 2 : 1) as eluent. The corresponding hydrobromide salts of the individual isomers were obtained according to the published method.[6,10] The major products were 2-chloro-4-(4'-methylpiperazin-1'-yl)pyrimidine (**15**), its 6-phenyl analogue (**17**), and 2-chloro-4-(4'-methylpiperazin-1'-yl)-6-(*p*-tolyl)pyrimidine-5-carbonitrile (**19**), the minor products being the corresponding 4-chloro-2-(4'-methylpiperazin-1'-yl) analogues (**16**, **18**, **20**) (Scheme 3). It is clear that 2,4-dichloropyrimidines (**1**, **3** and **9**) accept the nucleophile predominantly at the C-4 position, to yield the major isomers (**15**, **17** and **19**). The structures of the isomeric products were assigned unambiguously by proton nOe experiments. For example, the nOe showed strong enhancement of the methylene protons at the C-2' of the *N*-methylpiperazine moiety when H-5 of the pyrimidine was irradiated in both of the isomers **15** and **17**; in addition, the enhancement of *ortho*-phenyl protons at the 6-position in **17** was seen.

Experimental

^{1}H NMR (300 MHz), ^{13}C NMR (75 MHz) and nOe spectra were obtained at 25°C, in $CDCl_3$ unless otherwise stated, using $(CH_3)_4Si$ as an internal standard. Column chromatography was used for complete separation as indicated. Thin-layer chromatography was performed on precoated silica gel plates (60-F_{254} 0.2 mm) manufactured by E.M. Science Inc. using short wave ultra-violet light (254 nm) was used to detect the UV absorbing compounds. Elemental analyses were performed on a Perkin-Elmer 2400 series II CHN analyser by Central Laboratory Unit (CLU), UAE University. Melting points were determined on a Gallenkamp apparatus in Pyrex capillaries.

2,4-Dichloro-6-phenylpyrimidine (**3**): To 2,4-dichloropyrimidine (**1**) (0.01 mol, 1.49 g) in dry THF (40 ml), cooled to –70°C, phenyllithium (0.011 mol, 6.875 ml, 1.6 M) was slowly added under nitrogen with stirring for two hours at the same temperature and for another one hour at –30°C. The reaction mixture was allowed to warm to 0°C for 15 min. H_2O (0.24 ml, 15 mmol) in THF (3 ml) was added, followed by DDQ (2.75 g in 15 ml THF). The mixture was stirred at room temperature for 15 min., then cooled to 0°C and treated with hexanes (10 ml) followed by aqueous NaOH (10 ml, 3 M). The organic layer washed with water and dried over anhydrous Na_2SO_4, then evaporated to dryness under reduced pressure. The solid purified by column chromatography using 25% hexanes in CH_2Cl_2 afforded the pure product **3** (1.6 g, 71%), m.p. 82–84°C (lit.[11] m.p. 85–86°C, lit.[12] m.p. 83–86°C).

2-Chloro-4-(1',3'-dithian-2'-yl)pyrimidine (**7**): To 1,3-dithiane (10 mmol, 1.20 g) in dry THF (20 ml), cooled to –70°C, *n*-butyllithium (12 mmol, 0.80 g) was added under nitrogen. The reaction mixture was stirred at –70°C for 20 min. 2-Chloropyrimidine (**4**) (10 mmol, 1.14 g) in dry THF 20 ml was added dropwise with stirring at –70°C and stirring was continued for another hour at –30°C. The reaction was left at 0°C for 15 min., H_2O (0.24 ml, 15 mmol) in THF (3 ml) was added, followed by DDQ (2.75 g in 15 ml THF). The reaction mixture was stirred at room temperature for 15 min, cooled to 0°C and then treated with hexanes (10 ml) followed by NaOH (10 ml, 3 M). The organic layer was washed with water, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure until dry. The residual solid was purified by silica gel chromatography using 25% hexanes in CH_2Cl_2 and recrystallised from the same solvent to afford pure product **7** (1.2 g, 51%), m.p. 108–109°C. ^{1}H NMR: δ 8.63 (d, 1H, H-5, *J* = 4.8 Hz), 7.42 (d, 1H, H-6, *J* = 4.8 Hz), 5.12 (s, 1H, H-2'), 3.12–3.08 (m, 2H, H-4',4"), 3.02–2.98 (m, 2H, H-6',6"), 2.19–2.03 (m, 2H, H-5',5"). ^{13}C NMR: δ 170.1 (C-2), 161.2 (C-4), 160.2 (C-6), 117.6 (C-5), 49.5 (C-2'), 30.0 (C-4' and C-6'), 24.8 (C-5'). Anal. Calc. for $C_8H_9ClN_2S_2$ (232.75): C, 41.28; H, 3.90; N, 12.04; S, 27.55. Found: C, 41.30; H, 3.89; N, 12.10; S, 27.49%.

2-[(N,N-Dimethylaminoethyl)amino]-4-(1',3'-dithian-2'-yl) pyrimidine (**8**): To 2-chloro-4-(1',3'-dithian-2'-yl)pyrimidine (**7**) (1 mmol, 0.23 g) in dry ethanol (5 ml), *N,N*-dimethylethylenediamine (2 mmol, 0.16 g) was added and the reaction mixture was heated under reflux for 4 h, then cooled to room temperature. The solvent was evaporated under reduced pressure and the residue was dissolved in ether (20 ml) and washed with saturated aq. $NaHCO_3$ (2 × 15 ml), dried over anhydrous Na_2SO_4, then evaporated to dryness. The resulting product was purified by column chromatography (ether : hexanes : ethanol 2 : 2 : 1) to give **8** (0.17 g, 85%), m.p. 135–137°C. ^{1}H NMR: δ 8.26 (d, 1H, *J* = 5.1 Hz), 6.64 (d, 1H, *J* = 5.1 Hz), 5.75 (bs, 1H, NH, exchanged with D_2O), 5.03 (s, 1H, H-2'), 3.50–3.45 (m, 2H, H-4',4"), 3.03–2.99 (m, 2H, H-6',6"), 2.52–2.48 (m, 2H, CH_2), 2.24 (s, 6H, 2 *N*-CH_3), 2.16–1.97 (m, 2H, H-5',5"). ^{13}C NMR: δ 166.9 (C-4), 162.2 (C-2), 158.8 (C-6), 107.9 (C-5), 57.9 (CH_2), 51.8 (C-2'), 45.2 (2 *N*-CH_3), 38.9 (CH_2), 38.8 (C-6'), 30.9 (C-4'), 25.3 (C-5'). Anal. Calc for $C_{12}H_{20}N_4S_2$ (284.44): C, 50.67; H, 7.09; N, 19.70; S, 22.55. Found: C, 50.60; H, 7.11; N, 19.66; S, 22.52%.

2,4-Dichloro-6-aryl-5-pyrimidinecarbonitriles (**9**, **10**): These compounds were prepared from 2-mercapto-6-aryl-5-cyanopyrimidin-4-ones by using a reported procedure[13] and were crystallised from hexanes: CH_2Cl_2 (5 : 2).

2,4-Bis-(4'-methylpiperazin-1'-yl)pyrimidines (**11–14**), *typical procedure*

To 2,4-dichloropyrimidine (**1**) (1 mmol, 0.15 g) in dry ethanol (2 ml), *N*-methylpiperazine (2 mmol, 0.20 g) was added and the mixture was heated under reflux for 3 h, then cooled to room temperature. The solvent was evaporated under reduced pressure and the residue was dissolved in ether (20 ml). The solution was washed with saturated aq. $NaHCO_3$ (2 × 15 ml), dried over anhydrous Na_2SO_4, and then evaporated to dryness. The product was purified by column chromatography (ether : hexanes : ethanol 2 : 2 : 1) to give **11** (0.25 g, 89%) from CH_2Cl_2/hexanes, m.p. 105–107°C. ^{1}H NMR: δ 7.93 (d, 1H, H-6, *J* = 4.5 Hz), 5.85 (d, 1H, H-5, *J* = 4.5 Hz), 3.79 (t, 4H, 2 CH_2, *J* = 3.9 Hz), 3.60 (t, 4H, 2 CH_2, *J* = 3.9 Hz), 2.45 (t, 8H, 4 CH_2, *J* = 3.6 Hz), 2.33 (s, 6H, 2 *N*-CH_3). ^{13}C NMR: δ 162.3 (C-4), 161.5 (C-2), 156.5 (C-6), 92.8 (C-5), 55.0, 54.7 (2 *N*-CH_3), 46.2, 46.1 (4 CH_2), 43.7, 43.6 (4 CH_2). The hydrobromide salt of **11** was obtained from aq. ethanol in 94% yield, m.p. 280–283°C (decomp.). Anal. Calc. for $C_{14}H_{24}N_6$.2HBr (438.21): C, 38.37; H, 5.98; N, 19.18. Found: C, 38.21; H, 6.05; N, 18.98%.

In a similar way were obtained:

2,4-Bis-(4'-methylpiperazin-1'-yl)-6-phenylpyrimidine (**12**), yield 93%; m.p. 135–137°C (from 95% ethanol), from the dichloro compound **3**. ^{1}H NMR: δ 7.98 (m, 2H, phenyl), 7.43 (m, 3H, phenyl), 6.32 (s, 1H, H-5), 3.92 (t, 8H, 4 CH_2, *J* = 4.8 Hz), 2.50 (t, 8H, 4 CH_2, *J* = 4.8 Hz), 2.36 (s, 6H, 2 *N*-CH_3). ^{13}C NMR: δ 163.7 (C-4), 164.2 (C-2), 161.9 (C-6), 139.3 (C-1'), 129.5 (C-4'), 128.4 (C-2'), 126.9 (C-3'), 55.2, 54.8 (2 *N*-CH_3), 46.4, 46.2 (4 CH_2), 44.0, 43.8 (4 CH_2). The hydrobromide salt of **12** was obtained from aq. ethanol in 92% yield, m.p. >300°C; Anal. calc. for $C_{20}H_{28}N_6$.2HBr (514.31): C, 46.87; H, 5.88; N, 16.34. Found: C, 46.82; H, 5.96; N, 16.32%.

2,4-Bis-(4'-methylpiperazin-1'-yl)-6-(p-tolyl)pyrimidine-5-carbonitrile (**13**), yield 86%; m.p. 140–142°C (from 95% ethanol), from the dichloro compound **9**. ^{1}H NMR (DMSO-d_6): δ 7.71 (d, 2H, *J* = 5.1 Hz), 7.43 (d, 2H, *J* = 5.1 Hz), 3.79 (bs, 8H, 4 CH_2), 2.42 (m, 8H, 4 CH_2), 2.22 (s, 6H, 2 *N*-CH_3). ^{13}C NMR (DMSO-d_6): δ 171.0 (C-4), 164.1 (C-2), 159.1 (C-6), 140.3 (C-1'), 134.3 (C-4'), 128.6 (C-2'), 128.5 (C-3'), 119.1 (CN), 76.9 (C-5), 54.8 (2 *N*-CH_3), 46.4, 45.4, 45.3, 43.2 (8 CH_2), 20.7 (*p*-CH_3). The hydrobromide salt of **13** was obtained from aq. ethanol in 82% yield, m.p. >300°C. Anal. calc. for $C_{22}H_{29}N_7$.2HBr (551.10): C, 47.75; H, 5.65; N, 17.72. Found: C, 74.62; H, 5.81; N, 17.85%.

2,4-Bis-(4'-methylpiperazin-1'-yl)-6-(2-naphthyl)pyrimidine-5-carbonitrile (**14**), yield 75%; m.p. 203–205°C (from 95% ethanol), from the dichloro compound **10**. ^{1}H NMR: δ 8.36 (s, 1H, αH), 7.94–7.91 (m, 4H), 7.54–7.53 (m, 2H), 3.95 (t, 8H, *J* = 3.6 Hz), 2.57–2.47 (t, 4H, *J* = 3.6 Hz), 2.35 (s, 6H, 2 *N*-CH_3). ^{13}C NMR: δ 172.1, 165.1, 159.3, 134.6, 134.5, 132.8, 129.5, 128.9, 127.9, 127.7, 127.3, 126.3, 126.0, 120.1 (CN), 78.1 (C-5), 54.9 (2 *N*-CH_3), 47.1, 46.1 (4 CH_2), 45.9, 43.8 (4 CH_2). Anal. calc. for $C_{25}H_{29}N_7$ (427.54): C, 70.23; H, 6.84; N, 22.93. Found: C, 70.21; H, 6.90; N, 22.85%.

2-Chloro-4-(4'-methylpiperazin-1'-yl)pyrimidine (**15**) *and 4-Chloro-2(4'-methylpiperazin-1'-yl)pyrimidine* (**16**), *typical procedure*

2,4-Dichloropyrimidine (**1**) (10 mmol, 1.49 g) was stirred at 0°C in dry ethanol (30 ml), and *N*-methylpiperazine (20 mmol, 2.0 g) was added over 15 min. The solution was then allowed to warm to room temperature. The reaction was monitored by TLC (ether : hexanes 1 : 1). The solvent was removed on a rotary evaporator at room temp. The residue was dissolved in ether (20 ml), washed with saturated aq. $NaHCO_3$ (2 × 15 ml), and then dried over anhydrous Na_2SO_4. The resulting mixture of two isomeric compounds (**15**/**16**) in 5 : 1 ratio (85% combined yield) was separated by column chromatography (ether : hexanes : ethanol 2 : 2 : 1) to give the separated products as white solids. *Compound* **15**, m.p. 215–217°C. ^{1}H NMR: δ 8.03 (d, 1H, H-6, *J* = 6.0 Hz), 6.37 (d, 1H, H-5, *J* = 6.0 Hz), 3.67 (s, 4H), 2.47 (t, 4H, *J* = 4.8 Hz), 2.34 (s, 3H, *N*-CH_3); ^{13}C NMR: δ 162.7 (C-4), 160.9 (C-2), 157.3 (C-6), 101.2 (C-5), 54.5 (*N*-CH_3), 46.0 (2 × CH_2), 44.0 (2 × CH_2). Anal. Calc. for $C_9H_{13}ClN_4$.HBr (293.59): C, 36.82; H, 4.81; N, 19.08. Found: C, 37.30; H, 5.00; N, 19.20%. *Compound* **16**, m.p. 236–238°C; ^{1}H NMR: δ 8.12 (d, 1H, H-6, *J* = 3.9 Hz), 6.49 (d, 1H, H-5, *J* = 3.9 Hz), 3.84 (t, 4H, *J* = 3.6 Hz), 2.45 (t, 4H, *J* = 3.6 Hz), 2.33 (s, 3H, *N*-CH_3). Anal. Calc. for $C_9H_{13}ClN_4$.HBr (293.59): C, 36.82; H, 4.81; N, 19.08. Found: C, 37.39; H, 5.08; N, 19.48%.

2-Chloro-4-(4'-methylpiperazin-1'-yl)-6-phenylpyrimidine (**17**) and *4-Chloro-2-(4'-methylpiperazin-1'-yl)-6-phenylpyrimidine* (**18**): Similar treatment of the dichoropyrimidine **3** yielded a mixture of the two isomeric compounds **17** and **18** in 4 : 1 ratio (89% combined yield). Chromatography separated the isomers. *Compound* **17**, m.p. 105–107°C from CH_2Cl_2/hexanes. ^{1}H NMR: δ 7.94 (m, 2H), 7.45 (m, 3H), 7.77 (s, 1H, H-5), 3.75 (s, 4H), 2.50 (t, 4H, *J* = 5.1 Hz), 2.36 (s, 3H, *N*-CH_3). ^{13}C NMR: δ 163.6 (C-4), 168.6 (C-2), 161.0 (C-6), 136.8 (C-1'), 130.5 (C-4'), 128.7 (C-2'), 127.0 (C-3'), 54.5 (*N*-CH_3), 46.0 (2 CH_2), 44.1 (2 CH_2). Anal. Calc. for $C_{15}H_{17}ClN_4$ (288.78): C, 62.39; H, 5.93; N, 19.40. Found: C, 62.34; H, 5.97; N, 19.23%. The hydrobromide salt of **17** was obtained from aq. ethanol in 95% yield; m.p. 275–277°C (decomp.). Anal. Calc. for $C_{15}H_{17}ClN_4$.HBr (369.69): C, 48.91; H, 4.93; N, 15.22. Found: C, 48.76; H, 5.01; N, 15.03%. *Compound* **18**, m.p. 84–86°C from CH_2Cl_2/hexanes. ^{1}H NMR: δ 8.16 (m, 2H), 7.49 (m, 3H), 6.96 (s, 1H, H-5), 3.98 (t, 4H, *J* = 5.1 Hz), 2.73 (s, 3H, *N*-CH_3), 2.52 (t, 4H, *J* = 5.1 Hz). ^{13}C NMR: δ 166.0 (C-4), 161.9 (C-2), 161.8 (C-6), 136.7 (C-1'), 130.9 (C-4'), 128.7 (C-2'), 127.1 (C-3'), 54.9 (*N*-CH_3), 46.2 (2 CH_2), 43.9 (2 CH_2). Anal. Calc. for $C_{15}H_{17}ClN_4$ (288.78): C, 62.39; H, 5.93; N, 19.40. Found: C, 62.87; H, 6.16; N, 19.06%.

2-Chloro-4-(4'-methylpiperazin-1'-yl)-6-(p-tolyl)pyrimidine-5-carbonitrile (**19**) *and 4-Chloro-2-(4'-methylpiperazin-1'-yl)-6-(p-tolyl)pyrimidine-5-carbonitrile* (**20**): A mixture of two isomeric compounds **19** and **20** (5: 1) was isolated in 87% combined yield by similar treatment of the dichloropyrimidinecarbonitrile **9**, and was separated as before. Compound **19**, m.p. 115-117°C from CH_2Cl_2/hexanes. ^{1}H NMR: δ 7.83 (d, 2H, *J* = 7.6 Hz), 7.37 (d, 2H, *J* = 7.6 Hz), 3.89 (bs, 4H), 2.43(t, 4H, *J* = 3.9 Hz), 2.40 (s, 3H, N-CH_3), 2.24 (s, 3H, p-CH_3). ^{13}C NMR: δ 169.3 (C-4), 162.9 (C-2), 158.6 (C-6), 141.7 (C-1'), 132.4 (C-4'), 128.9 (C-2'), 128.4 (C-3'), 115.8 (CN), 91.6 (C-5), 53.7 (N-CH_3), 45.1 (2 CH_2), 43.6 (2 CH_2), 20.8 (p-CH_3). Anal. Calc. for $C_{17}H_{18}ClN_5$.HBr (408.72): C, 49.96; H, 4.69; N, 17.13. Found: C, 49.89; H, 4.75; N, 16.96%. Compound **20**, m.p. 96–99°C from CH_2Cl_2/hexanes. ^{1}H NMR: δ 7.75 (d, 2H, *J* = 6.3 Hz), 7.34 (d, 2H, *J* = 6.3 Hz), 3.90 (s, 4H), 2.46 (s, 4H), 2.39 (s, 3H, N-CH_3), 2.23 (s, 3H, p-CH_3); The hydrobromide salt of **20** (95%), m.p. >310°C (decomp.), was obtained from aq. ethanol. Anal. Calc. for $C_{17}H_{18}ClN_5$.HBr (408.72): C, 49.96; H, 4.69; N, 17.13. Found: C, 49.92; H, 4.77; N, 17.06%.

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