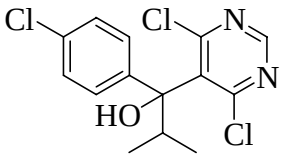
Supporting Information

Experimental

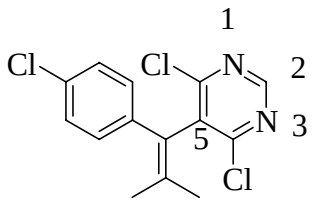
The presence of atropisomerism arising from diastereoisomerism is indicated in the ^{13}C spectra of the relevant compounds with the second isomer being indicated with an asterix (*).

***(4-Chlorophenyl)-1-(4,6-dichloro-4-pyrimidinyl)-2-methyl-1-propanol* 5b**



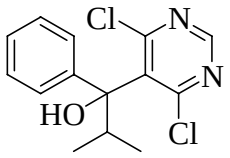
To a cold solution of freshly prepared lithium diisopropylamine [prepared from diisopropylamine (1.01 g, 10.0 mmol) and *n*-BuLi (6.25 ml of 1.6 M) in THF (10 ml) at -78 °C], was added solution of 4,6-dichloropyrimidine (1.5 g, 10.1 mmol) in THF (10 ml) added at -116 °C under nitrogen atmosphere. After stirring the reaction mixture for one 1 h at the same temperature, isobutyrophenone (1.84 g, 10.1 mmol) was added slowly, and stirring was continued for another 30 min. The reaction mixture was quenched with saturated ammonium chloride. The organic layer was separated, and the aqueous layer partitioned with DCM for (3 x 50 ml). The combined organic layers were first washed with dilute HCl, dried over $MgSO_4$ and evaporated under reduced pressure. The compound purified by flash silicagel chromatography (85:15 hexane:ethyl acetate) to give **5b** (1.33 g, 43%) as a white solid. mp 93-95 °C. ^1H NMR (300 MHz $CDCl_3$) δ: 8.58 (1H, s, H2), 7.41 (2H, d, J = 8.7 Hz, ArH2' and 6'), 7.31 (2H, d, J = 8.7 Hz, ArH3' and 5'), 3.54 (1H, m, C<u>H</u>$(CH_3)_2$), 3.32 (1H, s, OH), 1.07 (3H, d, J = 6.6 Hz, CH(C<u>H</u>$_3)_2$), 0.93 (d, J = 6.6Hz, CH(C<u>H</u>$_3)_2$). ^{13}C NMR ($CDCl_3$) δ: 161.2 (C4 and 6), 154.7 (C2), 141.9 (C5), 137.9 (ArC4'), 133.7 (ArC1') 128.4 (ArC2' and 6'), 128.2 (ArC3' and 5'), 82.0 (<u>C</u>-OH), 34.8, (<u>C</u>H$(CH_3)_2$); 18.5, (CH(<u>C</u>H$_3)_2$); 17.6, (CH(<u>C</u>H$_3)_2$). ES-MS *m/z*: 333 ($[M+1]^+$ ^{37}Cl, 100%), 331 ($[M+1]^+$, ^{35}Cl, 100); ES-HRMS *m/z*: calcd for $[M+1]^+$ $C_{14}H_{14}{}^{35}Cl_3N_2O$ 331.0178; found 331.0172.

4,6-Dichloro-5-[2-methyl-1-(4-chlorophenyl)-1-propenyl]pyrimidine 6b



To a solution of (4-chlorophenyl)-1-(4,6-dichloro-4-pyrimidinyl)-2-methyl-1-propanol **5b** (1.00 g, 3.0 mmol) in dichloromethane (10 ml) was slowly added thionyl chloride (0.35 g, 3.0 mmol, 0.22 ml). After stirring for 48 h at room temperature (25 °C), water was added slowly. The organic layer was separated and aqueous layer further partitioned with DCM (2 x 50 ml). The combined organic layers were washed with water (2 x 50 ml), dried over $MgSO_4$, the solvent evaporated under reduced pressure. The resultant residue purified by chromatography on silica (90:10 hexane:ethyl acetate) to give **6b** (0.74 g, 78%) as a white solid. mp 100-103 °C. ^{1}HNMR (300 MHz $CDCl_3$) δ: 8.70 (1H, s, H2), 7.31 (2H, d, J = 8.7 Hz, ArH2' and 6'), 7.22 (2H, d, J = 8.7 Hz, ArH3' and 5'), 1.90 (3H, s, C=C(C$\underline{H}_3$)$_2$), 1.67 (3H, s, (C=C(C$\underline{H}_3$)$_2$). ^{13}CNMR ($CDCl_3$) δ: 162.1 (C4 and 6), 156.4 (C2), 139.1 (C=C(CH$_3$)$_2$), 136.7 (ArC1'), 134.9 (C5), 133.4 (ArC4'), 131.1 (ArC2' and 6'), 128.5 (ArC3' and 5'), 126.7 (C=C(CH$_3$)$_2$), 22.3 (C=C(CH$_3$)$_2$), 21.7 (C=C(CH$_3$)$_2$). CI-MS *m/z*: 316 ([M+1]$^{+}$ ^{37}Cl, 20%), 314 ([M+]$^{+}$, ^{35}Cl, 95), 277 (65), 241 (50), 89 (100); EI-HRMS *m/z*: calcd for $C_{14}H_{11}{}^{35}Cl_3N_2O$ 311.997811; found 311.998782.

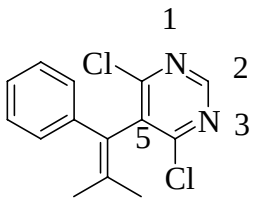
1-(4,6-Dichloro-4-pyrimidinyl)-2-methyl-1-phenyl-1-propanol **5a**



To a cold solution of freshly prepared lithium diisopropylamine [prepared from diisopropylamine (0.826 g, 8.18 mmol) and *n*-BuLi (.5235 ml of 1.6 M) in THF (10 ml) at -78 °C], was added a solution of 4,6-dichloropyrimidine (1.215 g, 8.20 mmol) was dissolved in THF (5 ml) at -116 °C under nitrogen atmosphere. After stirring the reaction mixture for one 1 h at the same temperature, isobutyrophenone (1.20 g 8.11 mmol) was added slowly, and stirring was continued for another 30 min. The reaction mixture was quenched with saturated ammonium chloride. The organic layer was separated, and the aqueous layer partitioned with DCM for (3 x 50 ml). The combined organic layers were first washed with dilute HCl, dried over $MgSO_4$ and evaporated under reduced pressure. The compound purified by flash silicagel chromatography (85:15 hexane:ethyl acetate) to give **5a** (1.0 g, 45%) as a white solid.

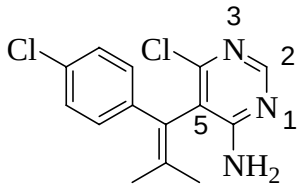
mp 66-68 °C. ^{1}H NMR (300 MHz $CDCl_3$) δ: 8.56 (s, H2), 7.46 (2H, d, J = 6.9 Hz, ArH2' and 6'), 7.35-7.26 (3H, m, ArH3', 4', and 5'), 3.57 (1H, m, C<u>H</u>$(CH_3)_2$), 3.39 (1H, s, OH), 1.07 (3H, d, J = 6.6Hz CH(C<u>H</u>$_3)_2$), 0.95 (3H, d, J = 6.6Hz CH(C<u>H</u>$_3)_2$). ^{13}C NMR ($CDCl_3$) δ: 161.2 (C4 and 6), 154.7 (C2), 143.4 (C5), 137.9 (ArC1') 128.2 (ArC2' and 6'), 127.8 (ArC4'), 126.7 (ArC3' and 5'), 82.4 (C-OH), 34.8 (<u>C</u>H$(CH_3)_2$), 18.5 (CH(<u>C</u>H$_3)_2$) 17.6 (CH(<u>C</u>H$_3)_2$). ES-MS *m/z*: 299 ([M+1]$^{+}$ ^{37}Cl, 65%), 297 ([M+1]$^{+}$, ^{35}Cl, 100), 279 (20), 242 (25); ES-HRMS *m/z*: [M+1]$^{+}$ calcd for $C_{14}H_{15}$ $^{35}Cl_2N_2O$ 297.0588; found 297.0561.

4,6-Dichloro-5-(2-methyl-1-phenyl-1-propenyl)pyrimidine 6a



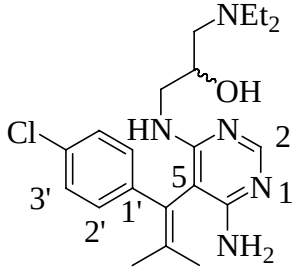
To a solution of phenyl-1-(4,6-dichloro-4-pyrimidinyl)-2-methyl-1-propanol **5a** (1.00 g, 3.4 mmol) in dichloromethane (10 ml) was slowly added thionyl chloride (0.4 g, 3.4 mmol, 0.25 ml). After stirring for 48 h at room temperature (25 °C) water was added slowly. The organic layer was separated and aqueous layer was further partitioned with DCM (2 x 50 ml). The combined organic layers were washed with water (2 x 50 ml), dried over $MgSO_4$, and the solvent evaporated under reduced pressure. The resultant residue was purified by flash silica gel chromatography (90:10 hexane:ethyl acetate) to give **6a** (0.76 g, 74%) as white solid. mp 73-75 °C. ^{1}H NMR (300 MHz $CDCl_3$) δ: 8.68 (1H, s, H2), 7.31-727 (5H, m, ArH2', 3', 4', 5', and 6'), 1.92 (3H, s, C=C(C<u>H</u>$_3)_2$), 1.68 (3H, s, (C=C(C<u>H</u>$_3)_2$). ^{13}C NMR ($CDCl_3$) δ: 162.1 (C4 and 6), 156.4 (C2), 138.4 (C5), 138.2 (<u>C</u>=C$(CH_3)_2$), 135.4 (ArC1'), 129.8 (ArC2' and 6'), 127.8 (ArC3' and 5'), 127.5 (ArC4'), 126.5 (C=<u>C</u>$(CH_3)_2$), 22.3 (C=C(<u>C</u>H$_3)_2$), 21.7 (C=C(<u>C</u>H$_3)_2$). CI-MS *m/z*: 281 ([M+1]$^{+}$ ^{37}Cl, 65%), 279 ([M+1]$^{+}$, ^{35}Cl, 100). EI-HRMS *m/z*: calcd for $C_{14}H_{13}{}^{35}Cl_2N_2$ 279.044452; found 279.045579.

4-Amino-6-chloro-5-[2-methyl-1-(4-chlorophenyl)-1-phenyl-1-propenyl]pyrimidine 7b



A suspension of 4,6-dichloro-5-[2-methyl-1-(4-chlorophenyl)-1-propenyl]pyrimidine **6b** (1.00 g, 3.2 mmol) in aqueous ammonia 20 ml (25%) was heated at 140 °C for 5 h in a glass sealed tube. The reaction mixture was cooled, the solid collected, washed with water and air dried. Recrystallisation from benzene produced **7b** (0.70 g. 75%) as white crystals, mp 208 °C. ^{1}H NMR (300 MHz $CDCl_3$) δ: 8.29 (1H, s, H2), 7.29 (2H, d, J = 8.7 Hz, ArH2' and 6'), 7.19 (2H, s, ArC3' and 5'), 5.23 (2H, s, NH_2), 1.96 (3H, s, C=C(CH_3)$_2$), 1.72 (3H, s, C=C(CH_3)$_2$); ^{13}C NMR ($CDCl_3$) δ: 162.1 (C6), 158.9 (C4), 157.0 (C2), 139.3 (C=C(CH_3)$_2$), 137.9 (ArC4'), 130.6 (ArC1'), 130.7 (ArC2' and 6'), 128.7 (ArC3' and 5'), 125.8 (C=C(CH_3)$_2$), 119.0 (C5), 22.5 (C=C(CH_3)$_2$), 22.1 (C=C(CH_3)$_2$); ES-MS *m/z*: 294 ([M+1]$^+$, ^{35}Cl, 50%), 260 (40), 241 (30).

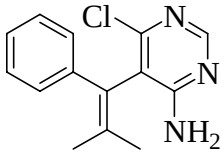
***1-[[6-Amino-5-[1-(4-chlorophenyl)-2-methylpropenyl]-4-pyrimidinyl]-3-(diethylamino)-2-propanol* 1**



A mixture of 4-amino-6-chloro-5-[2-methyl-1-(4-chlorophenyl)-1-phenyl-1-propenyl]pyrimidine **7b** (0.20 g, 0.7 mmol) and 1-amino-3-diethylamino-2-propanol (2 ml) was heated at 200 ºC for 5 h. The reaction mixture was cooled, the gummy residue was treated with between water and extracted with dichloromethane (3 x 50 ml). The combined organic extracts were dried over $MgSO_4$ and concentrated. The compound was purified by flash silica gel chromatography (70:20:10 ethyl acetate:methanol:water) affording **1** (0.11 g, 40%) as pale yellow solid. mp 127-129 °C. ^{1}H NMR (300 MHz $CDCl_3$) δ: 8.10 (1H, s, H2), 7.27 (2H, d, J = 8.7 Hz, ArH2' and 6'), 7.19 (2H, d, J = 8.7 Hz, ArH3' and 5'), 5.03 (1H, m, NH), 4.63 (2H, m, NH_2), 3.67 (1H, m, C<u>H</u>OH), 3.63-3.2 (2H, m, NHC<u>H</u>$_2$CHOH), 2.48 (4H, m, CH_2N(C<u>H</u>$_2$$CH_3$)$_2$), 2.35 (2H, m, C<u>H</u>$_2$N(CH_2CH_3)$_2$), 1.94 (3H, s, C=C(CH_3)$_2$), 1.76 (3H, s, C=C(CH_3)$_2$), 0.95 (6H, t, CH_2N(CH_2C<u>H</u>$_3$)$_2$). ^{13}C NMR ($CDCl_3$) δ: 159.7 (C6), 159.2 (C4), 156.9 (C2), 139.5 (C=C(CH_3)$_2$), 139.4* (C=C(CH_3)$_2$), 138.1 (ArC1'), 132.9 (ArC4'), 130.5 (ArC2' and

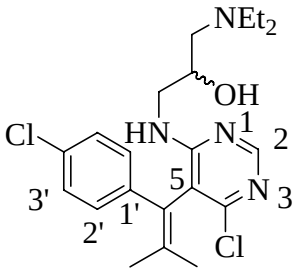
5'), 128.6 (ArC3' and 5'), 128.5* (ArC3' and 6'), 125.5 (C=<u>C</u>$(CH_3)_2$), 125.6* (C=<u>C</u>$(CH_3)_2$), 99.9 (C5), 67.1 (<u>C</u>HOH), 66.7* (<u>C</u>HOH), 56.5 (<u>C</u>H_2CHOH), 56.4* (<u>C</u>H_2CHOH), 47.4 ($CH_2N(\underline{C}H_2CH_3)_2$), 47.0* ($CH_2N(\underline{C}H_2CH_3)_2$), 44.8 ($\underline{C}H_2N(CH_2CH_3)_2$), 22.4 (C=C(<u>C</u>$H_3)_2$), 22.43* (C=C(<u>C</u>$H_3)_2$), 22.1 (C=C(<u>C</u>$H_3)_2$), 12.1 ($CH_2N(CH_2\underline{C}H_3)_2$), 11.9* ($CH_2N(CH_2\underline{C}H_3)_2$). CI-MS *m/z*: 404 ($[M+1]^+$, ^{35}Cl, 50%), 370 (15), 317 (15), 275 (60), 85 (100).

4-Amino-6-chloro-5-(2-methyl-1-phenyl-1-propenyl)pyrimidine 7a



A suspension of 4,6-dichloro-5-(2-methyl-1-phenyl-1-propenyl)pyrimidine **6a** (1.00 g, 3.6 mmol) in aqueous ammonia (20 ml) (25%) was heated at 140 °C for 5 h in a glass sealed tube. The reaction was cooled, the solid collected, washed with water and air dried. Recrystallisation from benzene produced **7a** (0.69 g, 74%) as a white crystals. mp 193 °C. ^{1}H NMR (300 MHz $CDCl_3$) δ: 8.25 (1H, s, H2), 7.33-7.21 (5H, m, ArH2', 3', 4', 5', and 6'), 5.66 (2H, s, NH_2), 1.96 (3H, s, C=C(C<u>H</u>$_3)_2$), 1.72 (3H, s, C=C(C<u>H</u>$_3)_2$); ^{13}C NMR ($CDCl_3$) δ: 162.5 (C6), 158.6 (C4), 156.7 (C2), 138.8 (<u>C</u>=C$(CH_3)_2$), 138.5 (C5) 130.4 (ArC2' and 6'), 128.4 (ArC3' and 5'), 127.4 (ArC4'), 126.9 (ArC1'), 118.8 (C=<u>C</u>$(CH_3)_2$), 99.9 (C5), 22.5 (C=C(<u>C</u>$H_3)_2$), 22.1 (C=C(<u>C</u>$H_3)_2$). ES-MS *m/z*: 262 ($[M+1]^+$ ^{37}Cl, 65%), 260($[M+1]^+$, ^{35}Cl, 100);

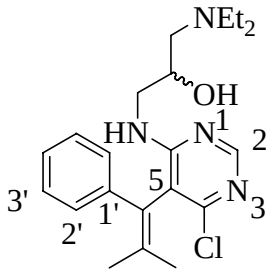
***1-[[6-Chloro-5-[1-(4-chlorophenyl)-2-methylpropenyl]-4-pyrimidinyl]-3-(diethylamino)-2-propanol* 8b**



A suspension of 4,6-dichloro-5-(2-methyl-1-phenyl-1-propenyl)pyrimidine **6a** (1.00 g, 3.2 mmol), 1-amino-3-diethylamino-2-propanol (2.33 g, 16.0 mmol) and potassium carbonate (0.44 g, 3.2 mmol) in THF (20 ml) was heated at 160 ºC for 12 h in a sealed glass reaction tube. The mixture was cooled, and the THF was evaporated to dryness. The residue was partitioned between water and dichloromethane (3 x 50 ml). The

combined organic extracts were dried over $MgSO_4$ and concentrated, and purified by flash silicagel column chromatography (80: 20 ethyl acetate: methanol) to yield **8b** (0.98 g, 73%) as a white hygroscopic solid. ^{1}H NMR (300 MHz $CDCl_3$) δ: 8.25 (1H, s, H2), 7.30 (2H, d, J = 8.7 Hz, ArH2' and 6'), 7.24 (2H, d, J = 8.7 Hz, ArH3' and 5'), 6.05 (1H, t, J = 5.7 Hz, NH), 4.10 (1H, m, C<u>H</u>OH), 3.77-3.39 (2H, m, NHC<u>H</u>$_2$CHOH), 2.99 (4H, m, $CH_2N(C\underline{H}_2CH_3)_2$), 2.92-2.47 (2H, m, $C\underline{H}_2N(CH_2CH_3)_2$), 1.93 (3H, s, $C=C(C\underline{H}_3)_2$), 1.72 (3H, s, $C=C(C\underline{H}_3)_2$), 1.12 (6H, t, $CH_2N(CH_2C\underline{H}_3)_2$). ^{13}C NMR ($CDCl_3$) δ: 161.3 (C6), 161.2* (C6), 157.3 (C4), 156.4 (C2), 156.3* (ArC2), 140.5 ($\underline{C}=C(CH_3)_2$), 140.2* ($\underline{C}=C(CH_3)_2$), 137.0 (ArC1'), 137.2 (C5), 133.0 (ArC4'), 130.8 (ArC2' and 6'), 130.83* (ArC2' and 6'), 128.42 (ArC3' and 6'), 128.40* (ArC3' and 6'), 125.1 ($C=\underline{C}(CH_3)_2$), 124.93* ($C=\underline{C}(CH_3)_2$), 65.8 (<u>C</u>HOH), 56.4 ($\underline{C}H_2CHOH$), 56.3* ($\underline{C}H_2CHOH$), 48.2 ($CH_2N(\underline{C}H_2CH_3)_2$), 44.8 ($\underline{C}H_2N(CH_2CH_3)_2$), 44.6* ($\underline{C}H_2N(CH_2CH_3)_2$), 22.13 ($C=C(\underline{C}H_3)_2$), 22.1* ($C=C(\underline{C}H_3)_2$), 21.8 ($C=C(\underline{C}H_3)_2$), 21.7* ($C=C(\underline{C}H_3)_2$), 9.5 ($CH_2N(CH_2\underline{C}H_3)_2$), 9.4* ($CH_2N(CH_2\underline{C}H_3)_2$); ES-MS *m/z*: 425 ($[M+1]^+$ ^{37}Cl, 65%), 423 ($[M+1, ^{35}Cl]^+$, 100). ES-HRMS *m/z*: calcd for $[M+1]^+$ $C_{21}H_{29}{}^{35}Cl_2N_4O$ 423.1723; found 423.1718.

1-[[6-Chloro-5-[1-phenyl-2-methylpropenyl]-4-pyrimidinyl]-3-(diethylamino)-2-propanol **8a**



A suspension of 4,6-dichloro-5-(2-methyl-1-phenyl-1-propenyl)pyrimidine **6a** (1.00 g, 3.6 mmol), 1-amino-3-diethylamino-2-propanol (2.62 g, 18.0 mmol) and potassium carbonate (0.50 g, 3.6 mmol) in THF (20 ml) was heated at 160 ºC for 12 h in a sealed glass reaction tube. The mixture was cooled, and the THF was evaporated to dryness. The residue was partitioned between water and dichloromethane (3 x 50 ml). The combined organic extracts were dried over $MgSO_4$, concentrated, and purified by flash silica gel column chromatography using (80: 20 ethyl acetate: methanol) to yield **8a** (1.00 g, 72%) as a colourless gummy substance. ^{1}H NMR (300 MHz $CDCl_3$) δ: 8.23 (1H, s, H2), 7.32-29 (5H, m, ArH2', 3', 4', 5', and 6'), 4.09 (1H, m, C<u>H</u>OH), 3.73-3.33 (2H, m, NHC<u>H</u>$_2$CHOH), 2.99 (4H, m, $CH_2N(C\underline{H}_2CH_3)_2$), 2.80-2.40 (2H, m,

C<u>H</u>$_2$N(CH$_2$CH$_3$)$_2$), 2.00 (3H, s, C=C(C<u>H</u>$_3$)$_2$), 1.92 (3H, s, C=C(C<u>H</u>$_3$)$_2$), 1.15 (6H, t, CH$_2$N(CH$_2$C<u>H</u>$_3$)$_2$). ^{13}C NMR ($CDCl_3$): δ 162.4 (C6), 161.95* (C6), 161.6 (C4), 161.4* (C4), 156.2 (C2), 156.1* (C2), 139.3 (<u>C</u>=C(CH$_3$)$_2$), 139.0 (ArC1'), 138.9 (C5), 127.7 (ArC2' and 6'), 127.0* (ArC2' and 6'), 126.3 (ArC3' and 5'), 125.4 (ArC4'), 124.3 (C=<u>C</u>(CH$_3$)$_2$), 63.3 (<u>C</u>HOH), 60.5 (<u>C</u>H$_2$CHOH), 55.7 (CH$_2$N(C<u>H</u>$_2$CH$_3$)$_2$), 44.9 (<u>C</u>H$_2$N(CH$_2$CH$_3$)$_2$), 44.8* (<u>C</u>H$_2$N(CH$_2$CH$_3$)$_2$), 21.4 (C=C(<u>C</u>H$_3$)$_2$), 21.3* (C=C(<u>C</u>H$_3$)$_2$), 8.8 (CH$_2$N(CH$_2$<u>C</u>H$_3$)$_2$), 8.7* (CH$_2$N(CH$_2$<u>C</u>H$_3$)$_2$); CI-MS *m/z*: 391 ([M+1]$^+$ ^{37}Cl, 70%), 389 ([M+1, ^{35}Cl]$^+$, 100). EI-HRMS *m/z*: calcd for $C_{21}H_{30}N_4O^{35}Cl$ 389.2113; found 389.2120.

^{13}C NMR spectrum of **1**, showing doubling of (most) peaks, arising from diastereoisomerism with one of the stereochemical elements due to atropisomeriem.