$$K_b = \frac{B}{\frac{EC_{50}'}{EC_{50}} - 1}$$

EC_{50}' = for IPNA in the presence of the reference concentration of the antagonist
EC_{50} = for IPNA in the control condition

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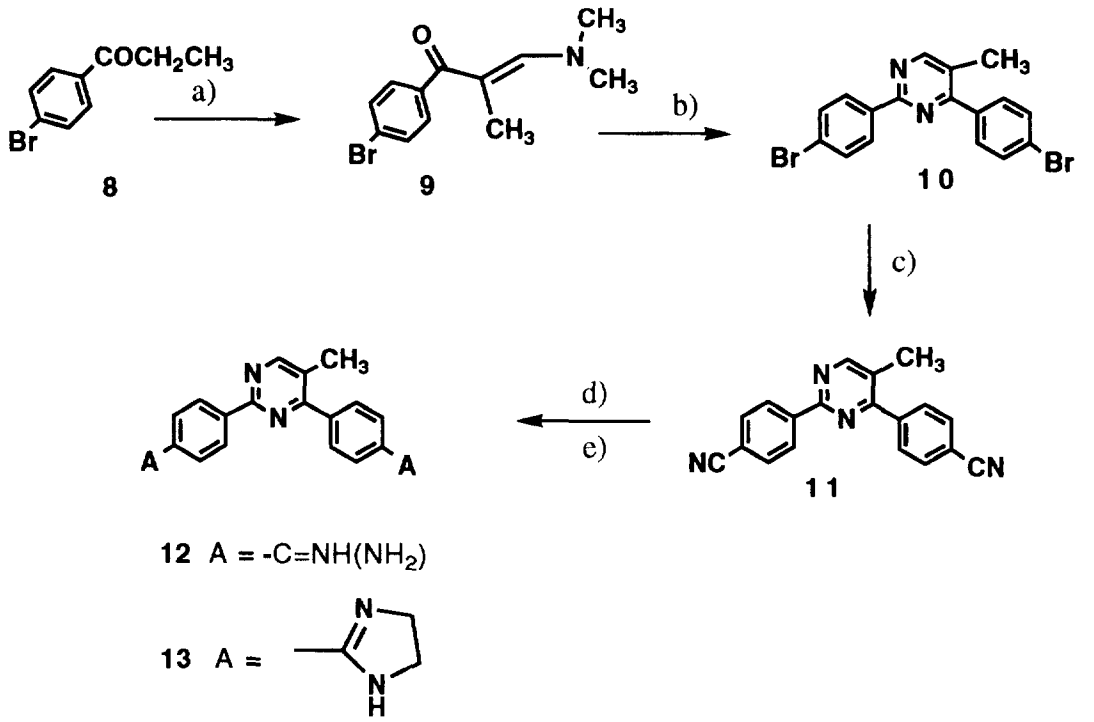
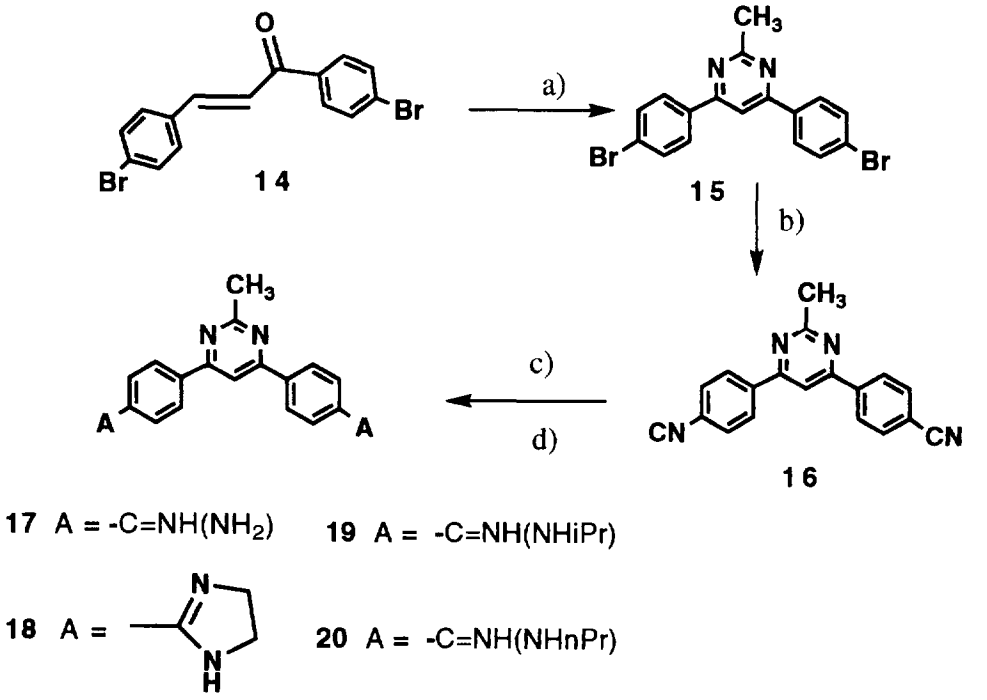


Scheme 2. (a) $(CH_3)_2NCH(OCH_3)$; (b) *p*-bromobenzamidine, NaOEt, EtOH; (c) CuCN, DMF; (d) HCl, EtOH; (e) NH_3 or $NH_2CH_2CH_2NH_2$.



Scheme 3. (a) Acetamidine, KOH; (b) CuCN, quinoline; (c) HCl, EtOH; (d) NH_3, $NH_2CH_2CH_2NH_2$, NH_2-*i*Pr or NH_2-*n*Pr.

Biological results and discussion

The results from the evaluation of the DNA binding characteristics using poly-dA•dT and the dodecamer d(CGCGAATTCGCG)$_2$ and the in vivo anti-PCP activity of the methyl pyrimidines are recorded in table I. All of the dicationic pyrimidines effectively bind to DNA as indicated by the ΔT_m values recorded in table I. The ΔT_m values for the compounds in the 2,4-bis-aryl-6-methylpyrimidines series (cf **5**–**7**) are in general close to the values noted for similar compounds in the parent series. Thus, as expected, the 6-methyl group essentially has no effect on minor-groove DNA binding. The ΔT_m values for the compounds in the 2,4-bis-aryl-5-methylpyrimidines series are clearly lower than those for the corresponding isomers in the 2,4-bis-aryl-6-methylpyrimidines series (compare results for **5** to **12** and **6** to **13**). The drop in DNA binding affinity is consistent with the greater twist of the 4-amidinophenyl group from the plane of the pyrimidine ring in **12** and **13**. Two of the three isomeric pairs (compare **5** to **17**; **6** to **18**; **7** to **19**) of the 4,6-bis-(aryl)-2-methylpyrimidines exhibit distinctly larger ΔT_m values suggesting that, in general, the slightly twisted diaryl array matches the curvature of the minor groove somewhat better than the more planar 2,4-bis-aryl-6-methylpyrimidine set.

The severely twisted diamidine **12** is less active against *Pneumocystis carinii* than either of the other isomeric analogs **5** and **17**. It is quite possible that the steric constraints of the DNA minor groove reduces the twist of the compounds on complex formation, but at a free energy cost that reduces the ΔT_m. The results in table I and those from previous studies [8, 12] indicate that the biological activity parallels the DNA binding affinity for these compounds. However, there is not a general correlation between DNA affinities and biological activity since several strong DNA binders (cf **19** and **20**) are not effective against *Pneumocystis carinii*. These findings support the model for anti-PCP activity of this type of dications: strong binding to the DNA of the microorganism is an essential requirement, but inhibiting of one or more DNA-associated enzyme is also required for biological activity.

Three of the dications **5**, **7** and **17** when screened at 5 mg/kg have comparable or improved anti-PCP activities compared to pentamidine, tested at 10 mg/kg, with apparently reduced overt toxicity. Further studies are underway to examine dose response effects for these compounds on activity and toxicity.

Table I. Biological evaluation of dicationic diaryl methylpyrimidines: in vivo activity against *P carinii*.

Compound	ΔT_m *(DNA)*[a]	ΔT_m *(oligo)*[b]	*Dosage*[c] *(mg/kg)*	*Toxicity*[c]	*Cyst/g lung* (10^6)[c] ± *SE*
Pentamidine	12.8	–	10	2+	0.73 ± 0.16
Saline	–	–	–	0	91.7 ± 16.0
5	18.8	5.5	5.0	1+	2.12 ± 0.88
6	21.3	6.0	2.5	2+	140.4 ± 35.4
7	18.8	5.0	5.0	0	0.09 ± 0.04
8	16.3	4.5	2.5	2+	108.8 ± 19.0
12	13.5	4.1	5.0	0	5.42 ± 3.12
13	14.9	4.5	ND[d]	ND[d]	ND[d]
17	21.5	10.5	4.4	0	0.32 ± 0.23
18	18.8	6.0	1.0	2+	33.0 ± 8.0
19	24.7	9.5	5.0	0	1.57 ± 1.51
20	23.0	9.0	5.0	0	32.9 ± 10.7

[a]Thermal melting increase of poly-dA•dT; see [15]. [b]Thermal melting increase of d(CGCGAATTCGCG)$_2$; see [15]. [c]Evaluation of iv dosage of the pyrimidines against *P carinii* in rats as described in [16]. [d]Not determined.

Experimental protocols

Melting points were recorded using a Thomas Hoover (Uni-Melt) capillary melting point apparatus or a Fisher-Johns melting point apparatus and are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were recorded employing a Varian GX400 or a Varian Unity*plus* 300 spectrometer and chemical shifts (δ) are in ppm relative to TMS; coupling constants are in hertz. High-resolution mass spectra were recorded with a VG Instruments 70-SE spectrometer (Georgia Institute of Technology, Atlanta, GA); others were recorded by a Shimadzu GC-MS 5000 instrument at 70 eV chamber voltage on a direct inlet system. IR spectra were recorded using a Michelson 100 (Bomem, Inc) instrument. Elemental analyses were obtained from Atlantic Microlab Inc (Norcross, GA) and are within $\pm 0.4\%$ of the theoretical values. All chemicals and solvents were purchased from Aldrich Chemical Co or Fisher Scientific. DNA ΔT_m values were determined as previously described [8].

1-(4-Bromophenyl)-3-(dimethylamino)-2-buten-1-one ***2***

A mixture of 4'-bromoacetophenone (19.9 g, 0.10 mol) and *N,N*-dimethylacetamide dimethyl acetal (19.95 g, 0.15 mol, 90%) was heated under reflux for 4 h during which time the color changed to dark red. The excess acetal was distilled, the residue was taken up in petroleum ether (40–60 °C bp) and on cooling a pinkish crystalline solid separated which was filtered, washed with hexane and recrystallized from ether/hexane (1:4) to yield an off-white solid, 22.0 g (83%), mp 112–113 °C. IR (KBr) 3069, 1608, 1561, 1462, 1203, 1072, 920, 768, 627, 506 cm^{-1}. ^{1}H-NMR ($CDCl_3$) 7.72 (d, 2H, J = 8.3), 7.49 (d, 2H, J = 8.3), 5.59 (s, 1H), 3.05 (s, 6H), 2.64 (s, 3H). ^{13}C-NMR ($CDCl_3$) 186.5, 164.2, 141.8, 131.0, 128.8, 124.5, 91.9, 40.0, 16.4. MS *m/e* 268 (M+). The 2-buten-1-one was used in the next step without further characterization.

2,4-Bis(4-bromophenyl)-6-methylpyrimidine ***3***

Sodium methoxide (0.92 g, 0.06 mol Na in 50 mL absolute methanol) was added to a stirred suspension of *p*-bromobenzamidine [12] (8.0 g, 0.04 mol) and 1-(4-bromophenyl)-3-(dimethylamino)-2-buten-1-one (9.64 g, 0.04 mol) in 75 mL absolute ethanol and the mixture was heated at reflux, under nitrogen, for 100 h. The excess solvent was distilled, the residue was treated with water, the solid was filtered, washed with water, dried, dissolved in $CHCl_3$ and dried over Na_2SO_4. The $CHCl_3$ was removed under vacuum and the residue was triturated by stirring at 50 °C for 20 min with 50–60 mL ethanol and the resultant solid filtered to yield white fluffy needles 12.0 g (50%), mp 160–161 °C. IR (KBr) 1585, 1529, 1483, 1362, 1669, 1007, 832, 781, 584 cm^{-1}. ^{1}H-NMR ($CDCl_3$) 8.41 (d, 2H, J = 8.31), 8.01 (d, 2H, J = 8.31), 7.62 (d, 2H, J = 6.35), 7.59 (d, 2H, J = 6.35), 7.38 (s, 1H), 2.6 (s, 3H). ^{13}C-NMR ($CDCl_3$) 167.5, 162.5, 161.7, 136.2, 135.2, 131.3, 130.8, 129.3, 128.0, 124.6, 124.5, 113.3, 23.8. MS *m/e* 404 (M+). 2,4-Bis(4-bromophenyl)-6-methylpyrimidine was used in the next step without further characterization.

2,4-Bis(4-cyanophenyl)-6-methylpyrimidine ***4***

A suspension of copper (I) cyanide (5.34 g, 0.06 mol) and 2,4-bis(4-bromophenyl)-6-methylpyrimidine (8.08 g, 0.02 mol) in 50 mL of dry DMF was heated at reflux, under nitrogen, for 20 h (TLC followed). The solvent was removed under vacuum and the residue was treated with 100 mL water, the suspension was poured into 300 mL of 10% aqueous NaCN and stirred for 3 h. The solid was filtered, washed with water, dried and subjected to soxlet extraction with acetone. The acetone solution was chromatographed over neutral Al_2O_3 to remove any remaining copper salts. The solid recovered from the eluent was crystallized from ether:$CDCl_3$ (4:1), to yield a white fluffy solid 4.38 g (74%) mp 262–263 °C. IR (KBr) 2223, 1580, 1366, 1222, 1010, 814, 781, 743, 588, 540 cm^{-1}. ^{1}H-NMR (DMSO-d_6/85 °C) 169.1, 161.9, 161.4, 141.4, 140.5, 132.7, 132.3, 128.4, 127.9, 118.2, 115.9, 113.7, 114.4, 24.2. MS *m/e* 296 (M+). Anal $C_{19}H_{12}N_4$ (C, H, N).

2,4-Bis-(4-amidinophenyl)-6-methylpyrimidine hydrochloride ***5***

The bis-nitrile **4** (2.96 g, 0.01 mol) was suspended in 80 mL of absolute ethanol, cooled in ice-salt bath and dry HCl gas was passed through it, and the compound dissolved. The clear yellow solution was placed in a pressure bottle and left for 24 h with occasional shaking. The imidate ester hydrochloride which formed was filtered, washed with dry ether and dried in vacuo to yield 3.6 g (73%). The dried imidate ester was demonstrated to be free of contamination of the bis-nitrile **4** by IR spectroscopy.

A suspension of imidate ester (0.6 g, 0.001 mol) prepared from 2,4-bis(4-cyanophenyl)-6-methyl pyrimidine and ethanol saturated with qaseous hydgrogen chloride, suspended in 15 mL absolute ethanol, was saturated with dry ammonia at 0–5 °C, the flask was securely closed and the mixture was stirred for 24 h at room temperature. The solvent was distilled under vacuum and the residue was suspended in ice–water, basified with 1 M NaOH to pH 10. The turbid mixture was extracted with chloroform, washed with water, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was recrystallized from ether/$CHCl_3$ (1:4) to a white solid 0.28 g (85%), mp 169–170 °C dec. ^{1}H-NMR (D_2O/DMSO-d_6/45 °C) 8.50 (d, 2H, J = 7.33), 8.31 (d, 2H, J = 7.33), 7.93–7.83 (m, 5H), 2.61 (s, 3H). MS *m/e* 330 (M+).

The free base of **5** (0.25 g, 0.00075 mol) in 5 mL ethanol was treated with 10 mL of saturated ethanolic-HCl, stirred for 1 h and the solvent was distilled. The residue was trituraed with ether, filtered, washed with ether and dried in vacuum at 70 °C for 12 h, to yield a white solid 0.3 g (87%) mp 263–265 °C dec. IR (KBr) 3365, 3295, 3151, 3018, 1675, 1635, 1533, 1487, 1310, 1090, 857, 780, 735 cm^{-1}. ^{1}H-NMR (D_2O/DMSO-d_6/45 °C) 8.70 (d, 2H, J = 8.79), 8.53 (d, 2H, J = 8.3), 8.07 (s, 1H), 8.05 (d, 2H, J = 8.3), 8.30 (d, 2H, J = 8.79), 2.70 (s, 3H). ^{13}C-NMR (D_2O/DMSO-d_6/45 °C) 170.1, 165.8, 165.7, 162.5, 162.1, 142.5, 141.6, 130.3, 130.1, 129.3, 129.0, 128.9, 128.3, 116.6, 24.6. Anal $C_{19}H_{18}N_6 \cdot 3HCl \cdot H_2O$ (C, H, N).

2,4-Bis-[(4-imidazolin-2-yl)phenyl]-6-methylpyrimidine hydrochloride ***6***

A mixture of ethylenediamine (0.18 g, 0.03 mol) and the bis imidate ester hydrochloride from **4** (0.6 g, 0.001 mol) in 15 mL of ethanol was heated at reflux, under nitrogen, for 12 h. A white solid separated and the solvent was removed. The solid was treated with water and the mixture was basified with 1 M NaOH to pH 10. The solid was filtered, washed with water, dried under vaccumm and recrystallized from ether/ethanol (4:1) to yield a white solid, 0.34 g (89%), mp 240–242 °C. ^{1}H-NMR (DMSO-d_6/D_2O/45 °C) 8.50 (d, 2H, J = 8.8), 8.31 (d, 2H, J = 8.30), 7.96 (d, 2H, J = 8.30), 7.93 (d, 2H, J = 8.30), 7.87 (s, 1H), 3.64 (s, 8H), 2.57 (s, 3H). ^{13}C-NMR (D_2O/DMSO-d_6/45 °C) 169.1, 164.2, 164.1, 162.9, 162.5,

139.6, 138.5, 132.4, 132.0, 128.2, 128.1, 127.4, 115.3, 49.5, 49.4, 24.3. MS *m/e* 382 (M^+).

The free base (0.30 g, 0.00078 mol) was dissolved in 10 mL ethanol and stirred with 10 mL saturated ethanolic HCl at 50 °C for 30 min. The solvent was distilled, the residue was triturated with dry ether to yield white solid. The solid was filtered, washed with ether and dried in vaccuum at 70 °C for 24 h to yield 0.32 g (89%) mp > 345 °C. IR (KBr) 3426, 3210, 3080, 2878, 1618, 1592, 1532, 1396, 1283, 1028, 850, 740, 677 cm^{-1}. ^{1}H-NMR (DMSO-d_6/D_2O) 8.59 (d, 2H, J = 8.79), 8.46 (d, 2H, J = 8.79), 8.16 (d, 2H, J = 8.3), 8.12 (d, 2H, J = 8.79), 8.0 (s, 1H), 4.02 (s, 8H), 2.6 (s, 3H). ^{13}C-NMR (D_2O/DMSO-d_6) 169.6, 164.6, 164.5, 161.8, 161.3, 142.5, 141.5, 129.5, 129.2, 128.6, 127.9, 124.2, 123.9, 116.3, 44.6, 24.3. Anal $C_{23}H_{22}N_6$•2HCl•0.7H_2O (C, H, N).

2,4-Bis[(4-N-isopropylamidino)phenyl]-6-methylpyrimidine hydrochloride ***7***

Freshly distilled isopropylamine (0.18 g, 0.003 mol) was added to a suspension of imidate ester hydrochloride from **4** (0.6 g, 0.001 mol) in 10 mL ethanol and stirred for 12 h at room temperature. The solvent was distilled, the residue was stirred with 20 mL dry-ether and decanted and treated with ice-water, basified with 1 M NaOH to pH 9. The precipitated solid was filtered, washed with water, dried (anhydrous Na_2SO_4) and crystallized form ether/chloroform (5:1) to yield a white solid 0.33 g (80%), mp 210–212 °C. ^{1}H-NMR (DMSO-d_6) 8.50 (d, 2H, J = 8.4), 8.31 (d, 2H, J = 8.4), 7.94 (s, 1H), 7.89 (d, 2H, J = 8.4), 7.85 (d, 2H, J = 8.4), 6.7–6.5 (br, 4H), 3.83 (sept, 1H, J = 6.5), 3.82 (sept, 1H, J = 6.5), 2.63 (s, 3H), 1.16 (d, 6H, J = 6.3), 1.55 (d, 6H, J = 6.3). MS *m/e* 414 (M^+).

The free base (0.3 g, 0.0007 mol) was dissolved in 8 mL saturated ethanolic HCl, and stirred for 30 min. The solvent was removed under vacuum and the residue was stirred with dry ether and the solid obtained was filtered, washed with ether and dried under vacuum at 70 °C for 24 h to yield 0.34 g (93%) white solid, mp 258–262 °C. IR (KBr) 3412, 3209, 3033, 2969, 1667, 1620, 1585, 1529, 1370, 1127, 1016, 850, 793, 743 cm^{-1}. ^{1}H-NMR (DMSO-d_6/D_2O) 8.62 (d, 2H, J = 8.3), 8.45 (d, 2H, J = 8.3), 8.01 (s, 1H), 7.89 (d, 2H, J = 8.79), 7.87 (d, 2H, J = 8.79), 4.06 (sept, 2H, J = 6.35), 2.63 (s, 3H), 1.29 (d, 12H, J = 6.35). ^{13}C-NMR (D_2O/DMSO-d_6) 169.7, 162.4, 162.0, 161.9, 161.8, 141.7, 140.7, 131.4, 131.2, 129.3, 129.0, 128.5, 127.8, 116.3, 45.6, 24.4, 21.4. Anal $C_{25}H_{30}N_6$•2HCl•H_2O (C, H, N).

2,4-Bis[(4-N-isopentylamidino)phenyl]-6-methylpyrimidine hydrochloride ***8***

Isoamylamine (0.26 g, 0.003 mol) was added to a suspension of imidate ester hydrochloride (0.6 g, 0.001 mol) from **4** in 15 mL absolute ethanol and stirred at room temperature for 12 h. The ethanol was removed and the residue treated with ice–water, basified with 1 M NaOH to pH 9 and the turbid mixture extracted with chloroform. The organic layer was washed with water, dried over Na_2SO_4. The solvent was removed under vacuum and the residue was triturated with dry ether. The solid was filtered, washed with ether and recrystallized form CH_2Cl_2/ether (1:4) to yield a white solid 0.4 g (85%), mp 183–185 °C. ^{1}H-NMR (DMSO-d_6) 8.50 (d, 2H, J = 8.55), 8.32 (d, 2H, J = 8.53), 7.93 (d, 1H), 7.92 (d, 2H, J = 8.55), 7.89 (d, 2H, J = 8.55), 6.45 (br, 4H), 3.16 (t, 4H, J = 3.66), 2.63 (s, 3H), 1.75 (sept, 2H, J = 6.72), 1.51 (m, 4H), 0.93 (d, 12H, J = 6.72). MS *m/e* 470 (M^+).

The free base (0.36 g, 0.0076 mol) was dissolved in 10 mL ethanolic HCl and stirred for 20 min. The solvent was distilled under vacuum and the residue was triturated with dry ether. The solid was filtered, washed with ether and dried under vacuum at 75 °C for 24 h to yield an off-white crystalline solid, 0.38 g (90%) mp 238–240 °C. IR (KBr) 3417, 3159, 3064, 2914, 1671, 1623, 1568, 1437, 1389, 1016, 741 cm^{-1}. ^{1}H-NMR (DMSO-d_6) 10.08 (brm, 2H), 9.74 (s, 1H), 9.7 (s, 1H), 9.37 (s, 1H), 9.35 (s, 1H), 8.67 (d, 2H, J = 8.5), 8.53 (d, 2H, J = 8.5), 8.15 (s, 1H), 8.02 (d, 2H, J = 8.5), 7.99 (d, 2H, J = 8.5), 3.50 (dt, 4H, J = 6.71), 2.68 (s, 3H), 1.75 (sept, 2H, J = 6.71), 1.60 (dt, 4H, J = 6.71), 0.96 (d, 1H). ^{13}C-NMR (D_2O/DMSO-d_6) 168.9, 162.2, 162.0, 161.8, 161.4, 141.2, 140.2, 130.9, 130.7, 128.9, 128.6, 127.8, 127.2, 115.7, 41.2, 35.8, 25.2, 23.9, 22.1. Anal $C_{29}H_{38}N_6$•2HCl•0.25H_2O (C, H, N).

1-(4-Bromophenyl)-2-methyl-3-(dimethylamino)propen-1-one ***9***

A mixture of 4-bromopropiophenone **8** (21.3 g, 0.1 mol) and *N,N*-dimethylformamide dimethyl acetal (23.8 g, 0.2 mol) was refluxed for 7 h with careful distillation of the methanol produced. The excess *N,N*-dimethylformamide dimethyl acetal was distilled off and the residual mass subjected to vacuum distillation to yield a dark brown thick oil, 18.7 g (70%). ^{1}H-NMR ($CDCl_3$) 7.47 (d, 2H, J = 8.3), 7.28 (d, 2H, J = 8.3), 6.82 (s, 1H), 3.05 (s, 6H), 2.11 (s, 3H). ^{13}C-NMR ($CDCl_3$) 195.3, 156.4, 142.7, 130.9, 129.8, 123.1, 105.8, 43.1, 10.9. MS 268 (M^+). Compound **9** was used directly in the next step without further characterization.

2,5-Bis(4-bromophenyl)-5-methyl-pyrimidine ***10***

Sodium ethoxide (0.06 mol, prepared from 1.38 g sodium in 75 mL absolute ethanol) was gradually added to a stirred suspension of *p*-bromobenzamidine benzene sulfonate (10.7 g, 0.03 mol) and 3-dimethylamino-1-(4-bromobenzoyl)-2-methylpropen-1-one (8.04 g, 0.03 mol) in 75 mL absolute ethanol and the reaction mixture was heated under reflux for 16 h (TLC monitored); the solvent was distilled off and the residue was treated with 150 mL water. The solid product was filtered, washed with water and dried. The product was dissolved in 250 mL chloroform, dried over anhydrous sodium sulfate, filtered, concentrated and recrystallized from chloroform/ether (1:4) to yield a white crystallized solid 7.75 g (64%), mp 136–137 °C. IR (KBr) 2381, 2346, 1588, 1533, 1484, 1429, 1099, 12009, 858, 756 cm^{-1}. ^{1}H-NMR ($CDCl_3$) 8.63 (s, 1H) 8.34 (d, 2H, J = 8.8), 7.63 (d, 2H, J = 8.8), 7.57 (d, 4H, J = 8.79), 2.37 (s, 3H). ^{13}C-NMR ($CDCl_3$) 163.7, 161.7, 159.5, 137.1, 136.5, 131.6, 131.6, 130.7, 129.6, 125.7, 125.1, 124.0, 17.0. MS 404 (M^+). Compound **10** was used directly in the next step without further characterization.

2,4-Bis-(4-cyanophenyl)-5-methylpyrimidine ***11***

A mixture of **10** (8.08 g, 0.02 mol) and cuprous cyanide (4.45 g, 0.05 mol) in 35 mL dry DMF was heated at reflux, under N_2, for 40 h (TLC monitored), the excess DMF was distilled using the vacuum from a water aspirator. The residual mass was treated with water and poured into 200 mL NaCN (aqueous) solution, and stirred for 3 h. The mixture was filtered, washed thoroughly with water, dried and subjected to soxlet extraction using acetone. The acetone was distilled off and the residue was dissolved into 75 mL $CHCl_3$ and chromatographed over neutral Al_2O_3 column; elution was with ether followed by 80:20 $CHCl_3$/ether to yield a white crystalline solid; yield (2.8 g, 48%), mp 194–195 °C. IR (KBr) 2226, 1608, 1581, 1509, 1426, 1211, 1110, 1073, 971, 906, 794 cm^{-1}.

^{1}H-NMR ($CDCl_3$) 8.78 (s, 1H), 8.6 (d, 2H, J = 5.83), 8.3 (d of d, 4H), 7.77 (d, 2H, J = 8.3), 2.45 (s, 3H). ^{13}C-NMR ($CDCl_3$) 163.2, 160.9, 160.0, 142.2, 141.3, 132.3, 132.2, 129.7, 128.5, 126.9, 118.7, 118.3, 113.9, 113.4, 16.9. MS *m/e* 296 (M^+). Anal $C_{19}H_{12}N_4$ (C, H, N).

2,4-Bis-(4-amidinophenyl)-5-methylpyrimidine ***12***

A suspension of imidate ester (0.6 g, 0.001 mol), prepared from 2,4-bis(4-cyanophenyl)-5-methyl pyrimidine and ethanol saturated with qaseous hydgrogen chloride, was suspended in 15 mL absolute ethanol and was saturated with dry ammonia at 0–5 °C, the flask was securely closed and the mixture was stirred for 24 h at room temperature. The solvent was distilled under vacuum and the residue was suspended in ice–water, basified with 1 M NaOH to pH 10. The mixture was extracted with chloroform, washed with water, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was recrystallized from ethanol to yield a white solid 0.25 g (77%), mp 192–195 °C dec. ^{1}H-NMR (D_2O/DMSO–d_6/60 °C) 8.89 (s, 1H), 8.50 (d, 2H, J = 8.4), 7.97 (d, 2H, J = 8.8), 7.93 (d, 2H, J = 8.8), 7.91 (d, 2H, J = 8.4), 2.41 (s, 3H). MS *m/e* 330 (M^+).

The free base of **12** (0.25 g, 0.00075 mol) in 5 mL ethanol was treated with 10 mL of saturated ethanolic-HCl, stirred for 1 h and the solvent was distilled. The residue was triturated with ether, filtered, washed with ether and dried in vacuum at 70 °C for 12 h, to yield a white solid 0.28 g (84%) mp 242–245 °C dec. IR (KBr) 3226, 1673, 1537, 1422, 1075, 860 cm^{-1}. ^{1}H-NMR (D_2O/DMSO–d_6/45 °C) 9.63 (br, 2H), 9.58 (br, 2H) 9.47 (br, 2H), 8.93 (s, 1H), 8.54 (d, 2H, J = 8.4), 8.08 (d, 2H, J = 8.4), 8.04 (d, 2H, J = 8.4), 7.98 (d, 2H, J = 8.4), 2.42 (s, 3H). ^{13}C-NMR (D_2O/DMSO–d_6/45 °C) 165.3, 162.9, 159.9, 142.4, 141.6, 129.4, 129.3, 128.6, 128.4 128.1, 127.6,127.5, 16.1. Anal $C_{19}H_{18}N_6$•3HCl•1.25H_2O (C, H, N).

2,4-Bis-[(4-imidazolin-2-yl)phenyl]-5-methylpyrimidine hydrochloride ***13***

The imidate ester hydrochloride from **11** (1.1 g, 0.0022 mol) was suspended into 25 mL of dry ethanol and to it was added ethylenediamine (0.39 g, 0.003 mol) and the mixture was heated at reflux for 12 h. The excess solvent was distilled off and the residue treated with cold water (50 mL) and the Ph was adjusted to ca 10 using 1 M NaOH. The white solid was filtered, washed with water, dried and crystallized from ethanol–ether to yield 0.63 g (75%), mp 127–129 °C. IR (KBr) 3392, 3288, 3166, 2971, 1602, 1549, 1421, 1278, 1108, 990, 855, 801 cm^{-1}. ^{1}H-NMR (DMSO–d_6/36 °C) 8.85 (s, 1H), 8.44 (d, 2H, J = 8.55), 7.98 (t, 4H), 7.83 (d, 2H, J = 6.93), 3.66 (s, 4H), 3.64 (s, 4H), 2.4 (s, 3H). ^{13}C-NMR (DMSO–d_6/35 °C) 163.5, 163.4, 163.3, 160.5, 159.6, 139.6, 139.0, 131.3, 130.6, 128.9, 127.5, 127.3, 127.1, 126.6, 49.1, 49.0, 16.4. MS *m/e* 382 (M^+).

To a solution of 0.38 g (0.001 mol) freebase in 10 mL absolute ethanol was added 5 mL of saturated ethanolic HCl and the mixture was heated under reflux (drying tube) for 20 min. After cooling, 75 mL dry ether was added and the salt filtered, washed with ether and dried in vacuum for 12 h at 60–70 °C to yield 0.48 g (83%), mp 244–245 °C. IR (KBr) 3446, 3191, 3108, 1600, 1377, 1284, 1074, 853 cm^{-1}. ^{1}H-NMR (DMSO–d_6/45 °C) 9.0 (s, 1H), 8.61 (d, 2H, J = 8.4), 8.39 (d, 2H, J = 8.4), 8.32 (d, 2H, J = 8.4), 8.08 (d, 2H, J = 8.4), 5.12 (br s, 5H), 4.08 (s, 4H), 4.06 (s, 4H), 2.46 (s, 3H). ^{13}C-NMR (DMSO–d_6/45 °C) 164.2, 164.1, 162.8, 160.1, 159.8, 142.9, 142.1, 129.7, 129.3, 128.9, 127.9, 123.7, 122.9, 44.3, 16.4. Anal $C_{23}H_{22}N_6$•3HCl•H_2O (C, H, N).

4,6-Bis(4-bromophenyl)-2-methylpyrimidine ***15***

1,3-Di(4-bromophenyl)propen-3-one **14**, prepared by a standard literature method [17] (10 g, 27.3 mmol) and dry acetamidine hydrochloride (1.29 g, 13.65 mmol) was dissolved in ethanol (500 mL) and a solution of potassium hydroxide (1.53 g, 27.3 mmol) in 100 mL ethanol was added. The reaction mixture was refluxed for 3 h, cooled and the solvent evaporated. Water was added to the residue and the suspension was extracted with ether. After drying, the ether was evaporated and the crude product was recrystallized from ethanol. Yield 3.4 g (61.5%) of white crystals, mp 169–170 °C. MS: *m/z* 402/404/406 (peaks in the molecular ion region). ^{1}H-NMR ($CDCl_3$): δ 8.01 (d, 4H, J = 8.8), 7.82 (s, 1H), 7.66 (d, 4H, J = 8.6), 2.85 (s, 3H). ^{13}C-NMR ($CDCl_3$): δ 168.8, 163.8, 136.2, 132.1, 128.7, 125.4, 109.1, 26.3. Anal $C_{17}H_{12}Br_2N_2$ (C, H, N).

4,6-Bis(4-cyanophenyl)-2-methylpyrimidine ***16***

A mixture of 4,6-bis(4-bromophenyl)-2-methylpyrimidine **15**, (3.36 g, 8.32 mmol) and copper(I)cyanide (1.88 g, 21 mmol) in freshly distilled quinoline (60 mL) was refluxed for 3 h. After cooling the reaction mixture was poured into ether (100 mL). The precipitate was collected by filtration, and washed with ether and water. After drying the solid was dissolved in acetone and passed through a short alumina column to remove copper and copper salts. The solvent was evaporated and the solid was crystallised from ethanol to yield 1.28 g (52%) of white fluffy needles, mp 276–277 °C. MS: *m/z* 296. ^{1}H-NMR (DMSO–d_6): δ 8.67 (s, 1H), 8.55 (d, 4H, J = 8.4), 8.07 (d, 4H, J = 8.4), 2.81 (s, 3H). ^{13}C-NMR (DMSO–d_6): δ 167.7, 162.4, 140.2, 132.2, 127.7, 117.9, 113.1, 110.9, 25.5. Anal $C_{19}H_{12}N_4$ (C, H, N).

4,6-Bis(4-amidinophenyl)-2-methylpyrimidine hydrochloride ***17***

The diimidate ester (1.34 g, 27 mmol) from **16** was suspended in absolute ethanol (50 mL), the suspension was chilled to 0–5 °C and saturated with NH_3 (g). The flask was stoppered and the content was stirred at room temperature for 3 d. Anhydrous ether was added to suspension and the solid was collected by filtration and washed with anhydrous ether. The free base was suspended in absolute ethanol saturated with HCl (25 mL) and heated at reflux for 1 h. After cooling, the solid was collected by filtration, washed with ether and acetone and dried in vacuum at 90 °C for 3 d to yield 0.54 g (72%) of white solid, mp > 290 °C. MS (FAB): *m/z* 331.1 (M^+ + 1). HRMS: calc mass (free base): 331.1671 (M^+ + 1); observed mass: 331.1687. ^{1}H-NMR (DMSO–d_6): δ 9.57 (br s, 4H), 9.30 (br s, 4H), 8.71 (s, 1H), 8.61 (d, 4H, J = 8.1), 8.06 (d, 4H, J = 8.1), 2.83 (s, 3H). ^{13}C-NMR (DMSO–d_6): δ 168.0, 165.0, 162.7, 140.9, 130.0, 128.7, 127.6, 111.1, 26.1. Anal $C_{19}H_{18}N_6$•2HCl•2H_2O (C, H, N).

4,6-Bis[4-(2-imidazolinyl)phenyl]-2-methylpyrimidine hydrochloride ***18***

The diimidate ester (1.34 g, 27 mmol) from **16** was suspended in absolute ethanol (50 mL) and ethylenediamine (0.22 g, 3.7 mmol) was added and mixture refluxed for 24 h. After cooling ether was added and the solid was filtered off and washed with anhydrous ether. The free base was suspended in ethanol saturated with HCl (25 mL) and heated at gentle reflux for 2 h. To the cooled mixture anhydrous ether was added and the solid was collected by filtration, washed with acetone and anhydrous ether and dried in vacuum at 90 °C for 3 d to yield

0.53 g (64%) of white solid, mp > 290 °C. MS (FAB): *m/z* 383.2 (M^+ + 1). HRMS: calc mass (free base): 383.1984 (M^+ + 1); observed mass: 383.1990. ^{1}H-NMR (DMSO-d_6): δ 10.90 (br s, 4H), 8.70 (s, 1H), 8.62 (d, 4H, *J* = 8.7), 8.26 (d, 4H, *J* = 8.7), 4.05 (s, 8H), 2.83 (s, 3H). ^{13}C-NMR (D_2O/DMSO-d_6): δ 170.0, 166.7, 164.9, 142.6, 130.2, 129.8, 125.5, 113.9, 46.2, 26.3. Anal $C_{23}H_{22}N_6$•2HCl•2H_2O (C, H, N).

4,6-Bis(4-N-isopropylamidinophenyl)-2-methylpyrimidine hydrochloride ***19***

The diimidate ester (1.00 g, 20 mmol) from **16** was suspended in absolute ethanol (50 mL) and isopropyl amine (2.1 mL, 25 mmol) was added. The mixture was stirred for 72 h at room temperature and ether was added. The solid which formed was collected by filtration and dried in vacuum at 90°C for 48 h. The free base was suspended in absolute ethanol saturated with HCl and refluxed for 2 h. After cooling dry ether was added and the solid collected by filtration, washed with acetone and dry ether, and dried in vacuum at 90 °C for 48 h. Yield 0.43 g (52%) of white powder, mp > 290 °C. MS (FAB): *m/z* 414.3 (M^+ + 1). HRMS: calc mass (free base): 414.2532 (M^+ + 1); observed mass: 414.2487. ^{1}H-NMR (DMSO-d_6): δ 9.70 (bs, 2H), 9.53 (bs, 2H), 9.13 (bs, 2H), 8.68 (s, 1H), 8.59 (d, 4H, *J* = 8.2), 7.93 (d, 4H, *J* = 8.5), 4.08 (m, 2H), 2.83 (s, 3H), 1.32 (d, 12H, *J* = 6.6). ^{13}C-NMR (DMSO-d_6): δ 168.3, 163.1, 161.4, 140.5, 131.4, 129.0, 127.7, 111.7, 45.3, 26.2, 21.3. Anal $C_{25}H_{30}N_6$•2HCl (C, H, N).

4,6-Bis(4-N-propylamidinophenyl)-2-methylpyrimidine hydrochloride ***20***

The diimidate ester from **16** was suspended in absolute ethanol (50 mL) and propylamine (0.39 g, 6.67 mmol) was added. The mixture was stirred for 72 h at room temperature and ether was added. The form solid was collected by filtration and dried in vacuum at 90 °C for 48 h. The free base was suspended in absolute ethanol saturated with HCl and refluxed for 2 h. After cooling, dry ether was added and the solid collected by filtration, washed with acetone and dry ether and dried in vacuum at 90 °C for 3 days. Yield 0.44 g (53%) of white powder, mp > 290 °C. MS (FAB): *m/z* 415.4 (M^+ + 1). HRMS: calc mass (free base): 415.2610 (M^+ + 1); observed mass: 415.2619. ^{1}H-NMR (DMSO-d_6): δ 10.0 (br s, 2H), 9.60 (br s, 2H), 8.69 (s, 1H), 8.60 (d, 4H, *J* = 8.1), 7.98 (d, 4H, *J* = 7.8), 3.43 (t, 4H, *J* = 7.1), 2.83 (s, 3H), 1.70 (m, 4H), 0.99 (t, 6H, *J* = 7.4). ^{13}C-NMR (D_2O/DMSO-d_6): δ 170.0, 165.4, 164.6, 142.0, 132.3, 129.7, 129.6, 114.0, 46.0, 26.3, 21.8, 12.0. Anal $C_{25}H_{30}N_6$•2HCl•0.5H_2O (C, H, N).

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