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Synthesis and antiproliferative activity of 2,6-diamino-9-benzyl-9-deazapurine and related compounds

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Abstract—Treatment of 6-bromomethyl- or 6-dibromomethyl-5-nitropyrimidine-2,4-diamine with KCN gave the same product—(2,6-diamino-5-nitropyrimidinyl)acetonitrile. Benzylation of the nitrile took place on the α-carbon to the cyano group preferentially affording the corresponding mono- and dibenzyl derivative, whose reductive cyclization resulted in 7-benzyl-5*H*-pyrrolo[3,2-*d*]pyrimidine-2,4-diamine and 7,7-dibenzyl-7*H*-pyrrolo[3,2-*d*]pyrimidine-2,4,6-triamine, respectively. Suitability of the protection of N^2 and N^4 atoms with benzyl, acetyl, or benzoyl groups was also investigated. The in vitro evaluation of cell growth inhibition on CCRF-CEM, HL-60, HeLa S3, and L1210 cell lines showed significant activity in 8 new compounds. The most potent compounds were the above mentioned 6-dibromomethyl derivative ($\mathrm{IC}_{50} = 0.54$, 1.7, 5.0, and 1.9 mol L^{-1}) and 7,N^2,N^4-tribenzyl-5*H*-pyrrolo[3,2-*d*]pyrimidine-2,4-diamine ($\mathrm{IC}_{50} = 1.9$, 2.7, 7.3, and 1.0 mol L^{-1}).

1. Introduction

In 1964, Imai reported preparation of 2,6-diamino-9-deazapurine and its activity against bacteria and protozoa.[1] Since that time, only a few of its derivatives with alkyl or aryl substituents on the amino groups[2,3] and, in a recent paper,[4] with *C*-phenyl group in the position 8 were described. Quite recently, we published the synthesis of 9-deaza analogue of cytokinin olomoucine, which bears *C*-methyl in position 9 (Ref. 5). Surprisingly enough, no 2,6-diamino-9-deazapurine counterpart to 9-arylmethyl-9-deazaguanines,[6,7] which are extremely potent inhibitors of purine nucleoside phosphorylase, have been synthesized so far. Therefore, our aim was to assess the synthetic availability of 2,6-diamino-9-arylmethyl-9-deazapurines as well as the potential of their biological activity.[8] To simplify our task we selected benzyl as the arylmethyl substituent, which could be introduced by alkylation of the appropriate 5-nitro-4(6)-(cyanomethyl)pyrimidines followed by reductive cyclization,[9–11] which is less laborious than the traditional approach based on pyrimidine ring construction on suitably substituted pyrroles introduced by Klein and co-workers.[12]

2. Results and discussion

Bromination of the starting 6-methyl-5-nitropyrimidine-2,4-diamine[13,14] (**1**) with 1 equiv of bromine in acetic acid according to the described procedure,[15,16] which provides a satisfactory monobromination of 2,4-dimethoxy-6-methyl-5-nitropyrimidine, results in this case in the 6-dibromomethyl derivative **2**. The desired monobromo derivative **3** was obtained in 7% yield only. This fact is due to much higher reactivity of the compound **3** in the bromination reaction compared to the starting compound **1**. With excess bromine, the dibromomethyl derivative **2** was obtained as the only product in high yield (Scheme 1). Reaction of compound **3** with potassium cyanide afforded the cyanomethyl derivative **4**. Surprisingly, dibromo derivative **2** gave with excess potassium cyanide also the nitrile **4** in a comparable yield. The mechanism of the reaction is unknown, nevertheless, TLC analysis showed in situ formation of the monobromo derivative **3**. The nitrile **4** is insoluble in organic solvents and water; therefore, its benzylation was carried out without isolation. The reaction afforded the *C*-benzyl derivative **5** as the main product.

Keywords: Pyrrolo[3,2-*d*]pyrimidines; Cytostatics; *Aci–nitro* Tautomerism; *C*-Alkylation; Reductive cyclization.

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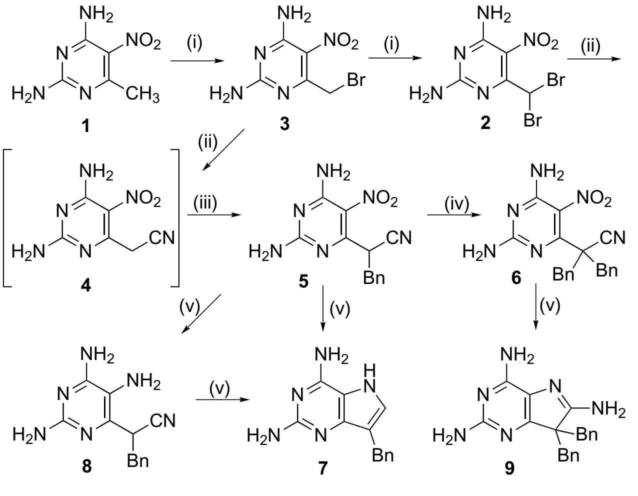
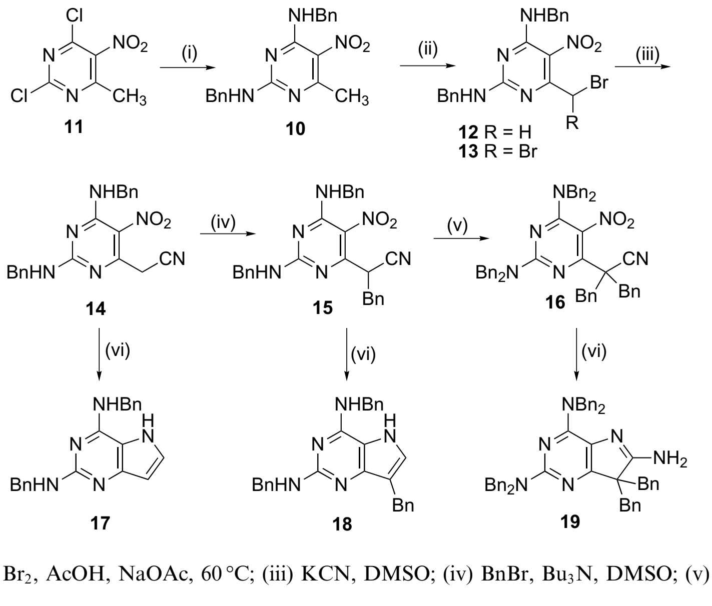


Scheme 1. (i) Br_2, NaOAc, AcOH; (ii) KCN, DMSO; (iii) BnBr, Bu_3N, DMSO; (iv) BnBr, KOH, dioxane–water 3:1, (v) H_2/Pd.

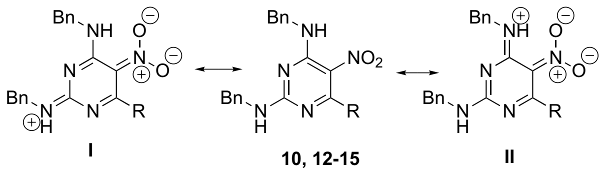
For further benzylation, compound **5** was treated with excess benzyl bromide in the presence of potassium hydroxide in a dioxane–water (3:1) mixture. This reaction afforded selectively the *C*,*C*-dibenzyl derivative **6**. The monobenzyl derivative **5** was reductively cyclized by catalytic hydrogenation to the 5*H*-pyrrolo[3,2-*d*]pyrimidine **7** (the nitrogen atom of the cyano group is liberated as ammonia). A small portion of the uncyclized intermediate **8**, which is unstable and spontaneously cyclizes to compound **7**, was also isolated. To the contrary, in the dibenzyl derivative **6** the nitrogen atom of the cyano group is transformed by catalytic hydrogenation to the amino group in position 6, which resulted in the formation of the 6-amino-7*H*-pyrrolo[3,2-*d*]pyrimidine **9**.

To avoid the difficult isolation of polar and insoluble pyrimidine-2,4-diamines, we used their N^2,N^4-dibenzyl derivatives instead (Scheme 2). N^2,N^4-Dibenzyl-6-methyl-5-nitropyrimidine-2,4-diamine (**10**) was prepared by treatment of 2,4-dichloro-6-methyl-5-nitropyrimidine[17] (**11**) with benzylamine. Similarly as in the previous case, the attempted monobromination gave the monobromo derivative **12** in 9% yield only, whereas the dibromomethyl derivative **13** prevailed. The nitrile **14** was prepared from the easily available dibromo derivative **13** on treatment with potassium cyanide. Alkylation of the nitrile **14** with benzyl bromide in the presence of tri-*n*-butylamine gave the *C*-benzyl derivative **15**. In ^1H as well as ^{13}C NMR spectra of compounds **10** and **12**–**15**, each signal of the mentioned compounds is accompanied by a minor one (ratio 4–5: 1), whose chemical shift is only slightly different, however, distinct enough to be distinguished (see Experimental). Following sodium deuteroxide addition this phenomenon disappeared. We assume that this doubling of the chemical shifts reflects the existence of *aci–nitro* tautomerism with minor isomer as the *aci*-form (tentative structure **I** and **II**, Scheme 3). Contrary to the benzyl derivative **5**, in compound **15** the reactivity of the remaining hydrogen atom of the acid carbon and the NH-groups toward alkylation is comparable. Further benzylation of **15** with 1 equiv of benzyl bromide led to a mixture of products in which the perbenzyl derivative **16** prevailed. Catalytic hydrogenation of compounds **14** and **15** afforded the 5*H*-pyrrolo[3,2-*d*]pyrimidines **17** and **18**, respectively, whereas the perbenzyl derivative **16** gave the 6-amino-7*H*-pyrrolo[3,2-*d*]pyrimidine **19**. No cleavage of *N*-benzyl groups by hydrogenation or by other debenzylation procedures occurred in both cases.[18]

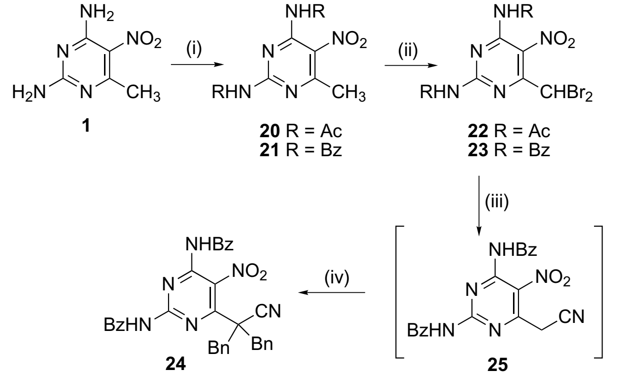
The impossibility to cleave the *N*-benzyl groups attached to pyrrolo[3,2-*d*]pyrimidine nucleus led us to examine, whether the acyl substituents in N^2 and N^4 positions could be used instead of benzyl groups to make the starting compound **1** more lipophilic (Scheme 4). The amino groups in compound **1** are not sufficiently nucleophilic due to the presence of the nitro group, however, refluxing of compound **1** with acetic anhydride



Scheme 2. (i) $BnNH_2$, K_2CO_3; (ii) Br_2, AcOH, NaOAc, 60 °C; (iii) KCN, DMSO; (iv) BnBr, Bu_3N, DMSO; (v) BnBr, NaH, DMSO; (vi) H_2/Pd.



Scheme 3.



Scheme 4. (i) Ac_2O, reflux or Bz_2O, 150 °C; (ii) Br_2, AcOH, NaOAc, 60 °C; (iii) KCN, DMSO; (iv) BnBr, NaH.

Table 1. Cytostatic activity of selected compounds

	IC_{50} ($\mu mol\,L^{-1}$)			
	CCRF-CEM	HL-60	HeLa S3	L1210
2	0.54	1.7	5.0	1.9
7	3.6	2.7	—	2.0
10	8.0	18.0	—	—
13	1.5	1.0	23.5	5.0
17	4.0	4.9	16.0	4.5
18	1.9	2.7	7.3	1.0
23	4.2	2.2	—	4.2
24	3.5	3.1	25.0	5.2

afforded the diacetate **20**. Similarly, melting compound **1** with benzoic anhydride at 150 °C gave the dibenzoate **21**. Treatment with excess bromine smoothly gave the 6-dibromomethyl derivatives **22** and **23**, respectively. However, their reaction with potassium cyanide gave a complex mixture of products. From the reaction mixture containing the dibromo derivative **23** and excess potassium cyanide in dimethyl sulfoxide, to which an excess of benzyl bromide was given, the dibenzyl derivative **24** was isolated in 9% yield only, which confirmed the in situ formation of the nitrile **25**.

In vitro cell growth inhibition by compounds **2**, **5**–**7**, **9**, **10**, **13**–**15**, **17**, **18**, and **20**–**24** was evaluated in the following cell lines:[19,20] human T-lymphoblastoids CCRF-CEM line (ATCC CCL 119), human promyelocytic leukemia HL-60 cells (ATCC CCL 240), human cervix carcinoma HeLa S3 cells (ATCC CCL 2.2), and mouse lymphocytic leukemia L1210 cells (ATCC CCL 219). For compounds, whose inhibition of the cell growth at $c = 10\,\mu M$ was higher than 30%, IC_{50} values were determined (Table 1).

3. Conclusion

The assay showed a potent antiproliferative activity of the 6-dibromomethyl-5-nitropyrimidines **2**, **13**, and **23**, which is slightly lower than the activity of 6-(dibromomethyl)-2-methoxy-4-morpholino-5-nitropyrimidine (L1210, $IC_{50} = 0.32\,\mu M$; H.Ep.2, $IC_{50} = 1.6\,\mu M$) and related compounds described by a Townsend's group.[16] However, the IC_{50} values of the 5-nitropyrimidines **10** and **24** show that the activity is not necessarily associated with the presence of dibromomethyl group. With regard to the in vivo toxicity of 6-dibromomethyl-5-nitropyrimidines,[16] the activity of the pyrrolo[3,2-*d*]pyrimidines **7**, **17**, and **18** seems to be more interesting. The mechanism of their cytostatic activity is so far unknown. The analysis of cell-cycle profiles (CCRF-CEM cells, G_1/G_0, $S+G_2/M$) at various concentrations of tested compounds (IC_{25}, IC_{50}, IC_{75}) by flow cytometry did not show any differencies between control and treated samples (data not shown). These results reveal a certain potential of substituted 2,6-diamino-9-deazapurines for the design of antineoplastic compounds.

4. Experimental

4.1. General

Melting points were determined on a Kofler block and are uncorrected. Analytical TLC was performed on silica gel pre-coated aluminum plates with fluorescent indicator (Merck 5554, 60 F_{254}). Spots were visualized with UV light (254 nm) or by spraying with ninhydrin (1% solution in ethanol) followed by a short heating to 300–400 °C. Column chromatography was carried out on silica gel (Sigma S-0507, 40–63 μm). Mass spectra were measured on a ZAB-EQ (Micromass, Manchester, UK) spectrometer using the EI (electron energy 70 eV) or FAB (ionization with Xe, accelerating voltage 8 kV, thioglycerol–glycerol 3:1 mixture or bis(2-hydroxyethyl) disulfide were used as matrix). ^1H and ^{13}C NMR spectra were recorded at 500 and 125.7 MHz on a Varian Unity 500 instrument in DMSO-d_6 (referenced to the solvent signal $\delta = 2.50$ and 39.70 ppm, respectively). Chemical shifts are in ppm and coupling constants (J) in Hz. UV spectra were taken on a Beckman DU-65 spectrophotometer in methanol solution. IR spectra were obtained on an FT IR Bruker Equinox IFS 55 spectrometer in chloroform or KBr pellets. Elemental analyses were carried out on a Perkin Elmer CHN Analyser 2400, Series II Sys (Perkin Elmer, Norwolk, CT USA).

4.2. Cytostatic activity assays

Inhibition of the cell growth was estimated in CCRF-CEM T-lymphoblastoid cells (human acute lymphoblasic leukemia, ATCC CCL 119), human promyelocytic leukemia HL-60 cells (ATCC CCL 240), human cervix carcinoma HeLa S3 cells (ATCC CCL 2.2), and mouse lymphocytic leukemia L1210 cells (ATCC CCL 219) (Ref. 19). CCRF-CEM, HL-60, and L1210 cells were cultivated in RPMI 1640 medium supplemented with

10% calf fetal serum using 24-well tissue culture plates. The endpoint of the cell growth was 72 h following the drug addition. HeLa S3 cells were seeded to 24-well dishes in RPMI 1640 HEPES modification with fetal calf serum. After 48 h following the drug addition the cultivation was stopped and the cell growth was evaluated. In parallel, the cell viability was examined using MTT standard spectrophotometric assay.[20] The inhibitory potency of the tested compounds was expressed as IC_{50} values.

4.2.1. 6-Dibromomethyl-5-nitropyrimidine-2,4-diamine (2). Compound **1** (3.4 g, 20 mmol) and sodium acetate (3.4 g, 41 mmol) were added to a solution of bromine (6.6 g, 41 mmol) in acetic acid (200 mL) and the reaction mixture was heated to 65 °C for 20 min. The solvent was evaporated to a small volume, taken into ethyl acetate and washed with water and brine. Chromatography on a silica gel column (chloroform–methanol 97:3) followed by crystallization (ethyl acetate) afforded compound **2** as yellow crystals (5.1, 78%) g, mp 185–187 °C. MS (EI) *m/z* (rel. intensity): 329 (29), 327 (59, M), 325 (31), 248 (35, M−Br), 246 (35, M−Br), 220 (28, M−Br–NO), 218 (31, M−Br–NO), 167 (58, M−Br_2), 57 (41), 43 (100). ^{1}H NMR (500 MHz, DMSO-d_6): 8.09 (s, 1H, NH), 7.98 (s, 1H, NH), 7.74 (s, 1H, NH), 7.47 (s, 1H, NH), 7.41 (s, 1H, $CHBr_2$). ^{13}C NMR (127.5 MHz, DMSO-d_6): 163.32 (C-6), 161.58 (C-4), 158.52 (C-2), 116.59 (C-5), 40.94 ($CHBr_2$). IR (KBr): 3501, 3383, 1649, 1608, 1545, 1421, 1336, 1267, 1199, 1149, 737, 516 cm^{-1}. UV/vis (MeOH): 360 ($\varepsilon = 9700$), 276 ($\varepsilon = 6400$). Anal. Calcd for $C_5H_5Br_2N_5O_2$:C, 18.37; H, 1.54; Br, 48.88; N, 21.42. Found: C, 18.19; H, 1.75; Br, 48.60; N, 21.19.

4.2.2. 6-Bromomethyl-5-nitropyrimidine-2,4-diamine (3) and 6-Dibromomethyl-5-nitropyrimidine-2,4-diamine (2). Compound **1** (3.4 g, 20 mmol) and sodium acetate (1.6 g, 20 mmol) were added to a solution of bromine (3.2 g, 20 mmol) in acetic acid (200 mL) and the reaction mixture was heated to 65 °C for 20 min. The solvent was evaporated to a small volume, taken into ethyl acetate and washed with water and brine. Chromatography on a silica gel column (chloroform–methanol 97:3) followed by crystallization (ethyl acetate) afforded, besides the unreacted starting compound **1** (1.2 g, 35%) and the dibromo derivative **2** (2.5 g, 38%), compound **3** (350 mg, 7%) as yellowish crystals, mp 142–143 °C. MS (EI) *m/z* (rel. intensity): 249 (8, M), 247 (8, M), 232 (5, M−NH_3), 230 (5, M−NH_3), 168 (100, M−Br). ^{1}H NMR (500 MHz, DMSO-d_6): 8.01 (s, 2H, NH), 7.56 (s, 1H, NH), 7.38 (s, 1H, NH), 4.60 (s, 2H, CH_2 Br). ^{13}C NMR (127.5 MHz, DMSO-d_6): 164.52 (C-6), 161.21 (C-4), 159.13 (C-2), 119.17 (C-5), 33.64 (CH_2 Br). Anal. Calcd for $C_5H_6BrN_5O_2$: C, 24.21; H, 2.44; Br, 32.21; N, 28.24. Found: C, 24.38; H, 2.63; Br, 31.98; N, 28.01.

4.2.3. 2-(2,6-Diamino-5-nitropyrimidin-4-yl)-3-phenylpropionitrile (5). To a suspension of potassium cyanide (1.6 g, 25 mmol) in dimethyl sulfoxide (125 mL) cooled to 0 °C compound **2** (1.6 g, 5 mmol) was added portionwise within 15 min and the reaction mixture was left at room temperature for additional 20 min. Benzyl bromide (6.0 g, 35 mmol) was added and the reaction mixture was stirred overnight. The reaction mixture was taken into ethyl acetate and washed with brine. Chromatography on a silica gel column (chloroform–methanol 98:2) followed by crystallization (petroleum ether–ethyl acetate 1:1) afforded compound **5** (580 mg, 41%) as yellowish crystals, mp 240–241 °C. MS (EI) *m/z* (rel. intensity): 284 (4, M), 267 (6), 178 (100, M−Bn–NH), 152 (11), 123 (18), 91 (87), 43 (28). ^{1}H NMR (500 MHz, DMSO-d_6): 8.04 (s, 1H, NH), 8.02 (s, 1H, NH), 7.66 (s, 1H, NH), 7.46 (s, 1H, NH), 7.35–7.30 (m, 5H, Ph), 5.05 (dd, 1H, $J = 10.5$, 4.5, C*H*–CN), 3.32 (dd, 1H, $J = 13.3$, 4.5, C*H*$_2$ Ph), 3.01 (dd, 1H, $J = 13.3$, 10.5, C*H*$_2$ Ph). ^{13}C NMR (125.7 MHz, DMSO-d_6): 163.19 (C-4), 161.04 (C-6), 158.83 (C-2), 137.28 (Ph), 129.19 (2C, Ph), 128.74 (2C, Ph), 127.33 (Ph), 119.83 (C-5), 119.32 (CN), 40.43 (*C*H–CN), 37.91 (*C*H$_2$–Ph). IR (KBr): 3469, 3419, 3353, 3199, 2258, 1662, 1602, 1560, 1547, 1473, 1429, 1271, 1226, 793, 699, 501 cm^{-1}. UV/vis (MeOH): 348 ($\varepsilon = 11400$), 260 ($\varepsilon = 6800$). Anal. Calcd for $C_{20}H_{18}N_6O_2$: C, 64.16; H, 4.85; N, 22.45. Found: C, 64.03; H, 4.84; N, 22.32. Anal. Calcd for $C_{13}H_{12}N_6O_2$: C, 54.93; H, 4.25; N, 29.56. Found: C, 54.69; H, 3.97; N, 29.33.

4.2.4. 2-Benzyl-2-(2,6-diamino-5-nitropyrimidin-4-yl)-3-phenylpropionitrile (6). Benzyl bromide (480 µL, 4 mmol) was added to a solution of compound **5** (280 mg, 1 mmol) and potassium hydroxide (340 mg, 6 mmol) in a dioxane–water mixture (3:1, 10 mL) and the reaction mixture was stirred overnight. Methanol (5 mL) was added, the reaction mixture was taken into ethyl acetate, washed with brine and evaporated. Chromatography on a silica gel column (chloroform) followed by crystallization (petroleum ether–ethyl acetate, 5:1) afforded compound **6** (240 mg, 64%) as yellow crystals, mp 237–238 °C. MS (EI) *m/z* (rel. intensity): 374 (4, M), 357 (7, M−NH_3), 344 (7, M−NO), 283 (10, M−Bn), 251 (67, M−Bn–O_2), 236 (9, M−Bn–NO_2+H), 177 (25, M−2Bn–O+H), 91 (100, Bn). ^{1}H NMR (500 MHz, DMSO-d_6): 7.59 (s, 2H, NH), 7.48 (s, 1H, NH), 7.39 (s, 1H, NH), 7.32–7.23 (m, 10H, Ph), 3.90 (d, 2H, $J = 13.4$, C*H*$_2$–Ph), 3.00 (d, 2H, $J = 13.4$, C*H*$_2$–Ph). ^{13}C NMR (500 MHz, DMSO-d_6): 161.25 (C-4), 160.45 (C-6), 158.26 (C-2), 135.51 (2C, Ph), 130.81 (4C, Ph), 128.25 (4C, Ph), 127.46 (2C, Ph), 122.21 (C-5), 118.95 (CN), 51.03 (*C*–CN), 42.53 (2C, *C*H$_2$–Ph). IR ($CHCl_3$): 3495, 3425, 2235, 1648, 1615, 1594, 1548, 1426, 1333, 1279 cm^{-1}. UV/vis (MeOH): 364 ($\varepsilon = 6000$), 265 ($\varepsilon = 7200$). Anal. Calcd for $C_{20}H_{18}N_6O_2$: C, 64.16; H, 4.85; N, 22.45. Found: C, 64.03; H, 4.84; N, 22.32.

4.2.5. 7-Benzyl-5*H*-pyrrolo[3,2-*d*]pyrimidine-2,4-diamine (7) Hydrochloride. 3-Phenyl-2-(2,5,6-triaminopyrimidin-4-yl)propionitrile (8). Compound **5** (570 mg, 2 mmol) in methanol (100 mL) acidified with methanolic hydrogen chloride (1 M, 5 mL) was hydrogenated under slight overpressure in the presence of Pd/C catalyst (10 wt %, 40 mg) overnight. The catalyst was filtered off through a

Celite pad and the filtrate evaporated. Chromatography on a silica gel column (chloroform–methanol, 96:4) followed by crystallization (ethyl acetate–methanol, 6:1) afforded hydrochloride of compound **7** (200 mg, 42%) as white crystals, mp 244–246 °C. MS (EI) *m*/*z* (rel. intensity): 240 (26, M+1), 239 (100, M), 238 (61, M−H), 223 (22, M−NH_2), 194 (19, M−NO_2+H), 162 (40, M−Ph). ^{1}H NMR (500 MHz, DMSO-d_6): 10.67 (s, 1H, NH), 7.25 (m, 4H, Ph), 7.15 (m, 1H, Ph), 7.05 (s, H-6), 6.80 (s, 2H, NH), 5.72 (s, 2H, NH), 3.05 (s, 2H, C*H*$_2$–Ph). ^{13}C NMR (500 MHz, DMSO-d_6): 157.33 (s, C-4), 151.73 (s, C-2), 144.05 (C-7a), 141.99 (Ph), 128.50 (2C, Ph), 128.32 (2 C, Ph), 125.98 (C-6), 125.74 (Ph), 111.50 (C-7), 109.425 (C-4a), 29.60 (*C*H$_2$–Ph). IR (KBr): 3326, 3186, 1636, 1560, 1543, 1472, 1396, 960 cm^{-1}. UV (MeOH): 287 ($\varepsilon = 11900$), 231 ($\varepsilon = 21400$). Anal. Calcd for $C_{13}H_{14}ClN_5$: C, 56.63; H, 5.12; Cl, 12.86; N, 25.40. Found: C, 56.91; H, 5.26; Cl, 12.59; N, 25.23.

The aforementioned chromatography afforded also a less polar uncyclized byproduct—compound **8** (30 mg, 6%), which was obtained by crystallization from ethyl acetate as white crystals with mp 182–184 °C. After several days storage it spontaneously cyclized to **7**. Data of compound **8**: MS (EI) *m*/*z* (rel. intensity): 254 (100, M), 238 (7, M−NH_2), 214 (18), 177 (20, M−Ph), 163 (61, M−Bn), 91 (97, Bn). ^{1}H NMR (500 MHz, DMSO-d_6): 7.35–7.25 (m, 5H, Ph), 6.24 (br s, 2H, NH_2), 5.43 (br s, 2H, NH_2), 4.56 (dd, $J = 9.8$, 6.2, C*H*–CN), 3.75 (br s, 2H, NH_2), 3.09 (dd, $J = 13.6$, 6.2, C*H*$_2$–Ph), 3.04 (dd, $J = 13.6$, 9.8, C*H*$_2$–Ph). ^{13}C NMR (125.7 MHz, DMSO-d_6): 157.845 (2C, C-2, C-6), 157.24 (C-4), 137.86 (Ph), 129.28 (2C, Ph), 128.84 (2C, Ph), 126.99 (Ph), 120.45 (CN), 114.16 (C-5). Anal. Calcd for $C_{13}H_{14}N_6$: C, 61.40; H, 5.55; N, 33.05. Found: C, 61.59; H, 5.76; N, 32.91.

4.2.6. 7,7-Dibenzyl-7*H*-pyrrolo[3,2-*d*]pyrimidine-2,4,6-triamine (9) dihydrochloride. Compound **6** (750 mg, 2 mmol) in methanol (100 mL) acidified with methanolic hydrogen chloride (1 M, 5 mL) was hydrogenated under slight overpressure in the presence of Pd/C catalyst (10 wt %, 40 mg) overnight. The catalyst was filtered off through a Celite pad and the filtrate evaporated. Chromatography on a silica gel column (chloroform–methanol, 97:3) followed by crystallization (ethyl acetate–methanol, 6:1) afforded dihydrochloride of compound **7** (530 mg, 58%) as white crystals, mp 199–201 °C. MS (EI) *m*/*z* (rel. intensity): 344 (26, M), 253 (48, M−Bn), 36 (100, HCl). ^{1}H NMR (500 MHz, DMSO-d_6): 11.40 (br s, 1H, NH), 10.88 (br s, 1H, NH), 8.40 (br s, 2H, NH_2), 7.53 (br s, 2H, NH_2), 7.23 (m, 6H, Ph), 7.07 (m, 4H, Ph), 3.81 (d, 2H, $J = 13.7$, C*H*$_2$–Ph), 3.75 (d, 2 H, $J = 13.7$, C*H*$_2$–Ph). ^{13}C NMR (500 MHz, DMSO-d_6): 169.31 (C-6), 153.92 (C-4), 151.34 (C-2), 146.90 (C-7a), 133.94 (2C, Ph), 129.06 (4C, Ph), 128.74 (4C, Ph), 127.89 (2C, Ph), 112.205 (C-4a), 61.35 (C-7), 40.935 (*C*$_2$–Ph). IR (KBr): 3303, 3110, 1658, 1550, 1516, 1497, 1457, 750, 703 cm^{-1}. UV (MeOH): 278 ($\varepsilon = 12600$). Anal. Calcd for $C_{20}H_{26}Cl_2N_6O_2$: C, 52.98; H, 5.78; Cl, 15.64, N, 18.54. Found: C, 52.88; H, 5.80; Cl, 15.47, N, 18.11.

4.2.7. *N*^{2},*N*^{4}-Dibenzyl-6-methyl-5-nitropyrimidine-2,4-diamine (10). 6-Methyl-5-nitrouracil (8.6 g, 50 mmol) was heated in aqueous sodium hydroxide (1 M, 50 mL) until a clear yellow solution arised. Water was evaporated under reduced pressure and the resulting sodium salt of 6-methyl-5-nitrouracil was co-evaporated with ethanol and toluene and dried in vacuo. The salt was added portionwise to phosphoryl chloride (50 mL, 540 mmol) at 0 °C and the reaction mixture was refluxed for 4 h. The resulting 2,4-dichloro-6-methyl-5-nitrouracil (**11**) was extracted from the reaction mixture with 3 portions (100 mL, each) of petroleum ether. Collected petroleum ether extracts were evaporated to a volume of about 60 mL, mixed with neutral aluminum oxide (10 g) and filtered through an aluminum oxide pad (10 g). Benzyl amine (approx. 15 mL) was added portionwise to the filtrate until it became basic. The alkalified filtrate was refluxed for 10 min, taken into ethyl acetate, washed with aqueous sodium hydrogen carbonate and brine. Chromatography on a silica gel column (chloroform) followed by crystallization (petroleum ether–ethyl acetate, 4:1) afforded compound **10** (9.4 g, 54%, yellow crystals, mp 117–118 °C [at 70–73 °C change of modification]) as a mixture of tautomers (5:1). MS (EI) *m*/*z* (rel. intensity): 349 (41, M), 332 (63, M−OH), 319 (9, M−NO), 301 (21), 243 (30, M−BnNH), 228 (7), 106 (17, BnNH), 91 (100, Bn). ^{1}H NMR (500 MHz, DMSO-d_6 *minor tautomer in italic*): 9.28 (t, 1H, $J = 6.1$, NH), *9.03 (t, 1H, J = 6.0, NH)*, 8.58 (t, 1H, $J = 6.5$, NH), *8.33 (t, 1H, J = 6.4, NH)* 7.40–7.10 (m, 10H, Ph), *7.40–7.10 (m, 10H, Ph), 4.70 (d, 2H, J = 6.0, CH*$_2$*–Ph*), 4.65 (d, 2H, $J = 6.1$, C*H*$_2$–Ph), *4.56 (d, 2H, J = 6.5, CH*$_2$*–Ph*), 4.43 (d, 2H, $J = 6.5$, C*H*$_2$4–Ph), *2.56 (s, 3H, CH*$_3$) 2.55 (s, 3H, CH_3). ^{13}C NMR (125.7 MHz, DMSO-d_6, *minor tautomer in italic*): *167.74 (C-6)*, 167.53 (C-6), *159.32 (C-4)*, 159.24 (C-4), 156.70 (C-2), *156.48 (C-2)*, *139.82 (Ph)*, 139.50 (Ph), 139.31 (Ph), *139.24 (Ph)*, *128.46 (2C, Ph)*, 128.42 (2C, Ph), *128.42 (2 C, Ph)*, 128.40 (2C, Ph), *127.75 (2C, Ph)*, 127.48 (2C, Ph), *127.59 (2C, Ph)*, 127.44 (2C, Ph), *127.03 (2C, Ph)*, 126.90 (2C, Ph), *121.76 (C-5)*, 120.78 (C-5), 44.38 (*C*H$_2$–Ph), *44.25* (*CH*$_2$*–Ph*), 44.14 (*C*H$_2$–Ph), *43.84* (*CH*$_2$*–Ph), 26.95* (*CH*$_3$), 26.53 (CH_3). IR ($CHCl_3$): 3436, 3366, 3019, 1591, 1568, 1546, 1510, 1435, 1346, 1266 cm^{-1}. UV/vis (MeOH): 362 ($\varepsilon = 16000$), 265 ($\varepsilon = 8100$), 224 ($\varepsilon = 19300$). Anal. Calcd for $C_{19}H_{19}N_5O_2$: C, 65.32; H, 5.48; N, 20.04. Found: C, 65.14; H, 5.40; N, 19.95.

4.2.8. *N*^{2},*N*^{4}-Dibenzyl-6-bromomethyl-5-nitropyrimidine-2,4-diamine (12). Compound **10** (700 mg, 2 mmol) and sodium acetate (160 g, 2 mmol) were added to a solution of bromine (320 mg, 2 mmol) in acetic acid (20 mL) and the reaction mixture was heated to 65 °C for 20 min. The solvent was evaporated to a small volume, taken into ethyl acetate and washed with water and brine. Chromatography on a silica gel column (petroleum ether–ethyl acetate 9:1) followed by crystallization (petroleum ether–ethyl acetate 19:1) afforded, besides the unreacted starting compound **10** (210 mg, 30%) and the dibromo derivative **13** (360 mg, 36%), compound **12** (80 mg, 9%, yellow crystals, mp 118–120 °C) as a mixture of 2 tautomers (5:1). MS (EI) *m*/*z* (rel. intensity): 429 (15, M), 427 (15, M), 349 (25, M−Br), 333 (23, M−Br–O), 332 (27, M−Br–OH), 301 (12), 243 (14), 106 (19, BnNH), 91 (100, Bn). ^{1}H NMR (500 MHz, DMSO-d_6 *minor tautomer in italic*): 9.41 (t, 1H, $J = 6.1$, NH), *9.29 (t, 1H,* $J = 6.1$, *NH*), 8.83 (t, 1H, $J = 6.5$, NH), *8.58 (t, 1H,* $J = 6.4$, *NH*), 7.40–7.10 (m, 10H, Ph), *7.40–7.10 (m, 10H, Ph), 4.70 (s, 2 H, CH$_2$Br), 4.69 (d, 2H,* $J = 6.1$, *CH$_2$Ph)*, 4.67 (d, 2H, $J = 6.1$, C*H*$_2$–Ph), 4.64 (s, 2H, CH$_2$Br), *4.58 (d, 2 H,* $J = 6.5$, C*H$_2$Ph*), 4.44 (d, 2H, $J = 6.5$, C*H*$_2$–Ph). ^{13}C NMR (125.7 MHz, DMSO-d_6 *minor tautomer in italic*): 164.54 (C-6), *164.50 (C-6) 159.39 (C-4)*, 159.21 (C-4), 156.78 (C-2), *156.54 (C-2)*, 139.13 (Ph), 139.04 (Ph), 128.48–126.90 (10C, Ph), *120.10 (C-5)*, 119.03 (C-5), 44.50 (*C*H$_2$–Ph), *44.37* (*CH$_2$–Ph*), *44.16* (*CH$_2$–Ph) 44.06* (*CH$_2$–Ph), 34.62* (*CH$_2$Br)*, 34.05 (CH$_2$Br). Anal. Calcd for $C_{19}H_{18}BrN_5O_2$: C, 53.28; H, 4.24; Br, 18.66; N, 16.35. Found: C, 53.19; H, 4.41; Br, 18.85; N, 16.12.

4.2.9. *N*^{2},*N*^{4}-Dibenzyl-6-dibromomethyl-5-nitropyrimidine-2,4-diamine (13). Compound **10** (7.0 g, 20 mmol) and sodium acetate (3.3 g, 40 mmol) were added to a solution of bromine (6.4 g, 40 mmol) in acetic acid (200 mL) and the reaction mixture was heated to 65 °C for 20 min. The solvent was evaporated to a small volume, taken into ethyl acetate and washed with water and brine. Chromatography on a silica gel column (petroleum ether–ethyl acetate 9:1) followed by crystallization (petroleum ether–ethyl acetate 19:1) afforded compound **13** (6.6 g, 65%, yellow crystals, mp 130–131 °C) as a mixture of 2 tautomers (4:1). MS (EI) *m*/*z* (rel. intensity): 509 (1.5), 507 (3), 505 (1.5) [M]; 492 (1.5), 490 (3), 488 (1.5) [M−OH]; 229 (1.5), 227 (1.5) [M−Br]; 421 (2), 410 (2) [M−Br–O]; 403 (1), 401 (2), 399 (1) [M−BnNH]; 106 (96) [BnNH]; 105 (68) [BnN]; 91 (100) [Bn]. ^{1}H NMR (500 MHz, DMSO-d_6, *minor tautomer in italic*): 9.35 (t, 1H, $J = 6.0$, NH), *9.12 (t, 1H,* $J = 6.0$, *NH),* 9.03 (t, 1H, $J = 6.5$, NH), *8.71 (t, 1H,* $J = 6.5$, *NH), 7.51 (s, 1H, CHBr$_2$)*, 7.50 (s, 1H, CHBr$_2$), 7.40–7.10 (m, 10H, Ph), *7.40–7.10 (m, 10H, Ph) 4.69 (d, 2H,* $J = 6.0$, *CH$_2$–Ph)*, 4.68 (d, 2H, $J = 6.0$, C*H*$_2$–Ph), *4.62 (d, 2H,* $J = 6.5$, *CH$_2$-Ph)*, 4.43 (d, 2H, $J = 6.5$, C*H*$_2$–Ph). ^{13}C NMR (125.7 MHz, DMSO-d_6, *minor tautomer in italic*): 163.34 (C-6), *163.01 (C-6), 159.57 (C-4)*, 159.46 (C-4), 156.19 (C-2), *156.11 (C-2), 139.45 (Ph)*, 139.01 (Ph), 138.87 (Ph), *138.81 (Ph)*, 128.43 (4C, Ph), *128.27 (4C, Ph), 127.75 (4C, Ph)*, 127.63 (2C, Ph), 127.40 (2C, Ph), *127.19 (Ph), 127.06 (Ph)*, 127.015 (Ph), 126.945 (Ph), *117.25 (C-5)*, 116.53 (C-5), 44.58 (2C, *C*H$_2$–Ph), *44.28 (2C, CH$_2$Ph*), 41.91 (CHBr$_2$), 41.17 (CHBr$_2$). IR (CHCl$_3$): 3430, 3375, 1593, 1584, 1569, 1546, 1508, 1278 cm^{-1}. UV/vis (MeOH): 379 ($\varepsilon = 12800$), 288 ($\varepsilon = 7200$). Anal. Calcd for $C_{19}H_{17}Br_2N_5O_2$: C, 45.00; H, 3.38; Br, 31.51; N, 13.18. Found: C, 45.06; H, 3.52; Br, 31.65; N, 13.38.

4.2.10. [2,6-Bis(benzylamino)-5-nitropyrimidin-4-yl]acetonitrile (14). To a suspension of potassium cyanide (3.2 g, 50 mmol) in dimethyl sulfoxide (150 mL) cooled to 0 °C compound **12** (5.1 g, 10 mmol) was added portionwise during 15 min and the reaction mixture was left at room temperature for additional 20 min. Acetic acid (5 mL) was added at 0 °C, the reaction mixture was taken into ethyl acetate and washed with brine. Chromatography on a silica gel column (petroleum ether–ethyl acetate 9:1) followed by crystallization (petroleum ether–ethyl acetate 4:1) afforded compound **14** (3.2 g, 87%, yellow crystals, mp 172–173 °C) as a mixture of 2 tautomers (3.8:1). MS (EI) *m*/*z* (rel. intensity): 374 (34, M), 357 (51, M−OH), 268 (14, M−BnNH), 256 (19), 91 (100, Bn). ^{1}H NMR (500 MHz, DMSO-d_6, *minor tautomer in italic*): 9.43 (t, 1H, $J = 6.0$, NH), *9.21 (t, 1H,* $J = 6.1$, *NH)*, 8.86 (t, 1H, $J = 6.4$, NH), *8.66 (t, 1H,* $J = 6.5$, *NH)*, 7.40–7.10 (m, 10H, Ph), *7.40–7.10 (m, 10H, Ph), 4.70 (d, 2H,* $J = 6.1$, *CH$_2$–Ph*), 4.68 (d, 2H, $J = 6.0$, C*H*$_2$–Ph), *4.61(d, 2H,* $J = 6.5$, *CH$_2$–Ph), 4.51 (s, 2H, CH$_2$CN*), 4.43 (d, 2H, $J = 6.4$, C*H*$_2$–Ph), 4.42 (s, 2H, CH$_2$CN). ^{13}C NMR (125.7 MHz, DMSO-d_6, *minor tautomer in italic*): *161.07 (C-4)*, 160.81 (C-4), *158.90 (C-6)*, 158.83 (C-6), 156.54 (C-2), *156.43 (C-2), 139.51 (Ph)*, 139.14 (Ph), 139.04 (Ph), *138.97 (Ph), 128.46 (4C, Ph)*, 128.44 (2C, Ph), 128.41 (2C, Ph), *128.10 (2C, Ph), 127.71 (2C, Ph)*, 127.54 (2C, Ph), 127.41 (2C, Ph), *127.18 (Ph), 127.06 (Ph)*, 126.99 (Ph), 126.954 (Ph), 119.62 (CN), *118.86 (CN)*, 116.98 (C-5), *116.92 (C-5), 44.65* (*C*H$_2$–Ph), *44.52* (*C*H$_2$–Ph), *44.43 (CH$_2$–Ph)*, 44.27 (*C*H$_2$–Ph), *29.20* (*CH$_2$–CN*), 28.53 (*C*H$_2$–CN). IR (CHCl$_3$): 3430, 3020, 2260, 2191, 1594, 1574, 1553, 1514, 1304, 1196 cm^{-1}. UV/vis (MeOH): 363 ($\varepsilon = 16400$), 269 ($\varepsilon = 7800$). Anal. Calcd for $C_{20}H_{18}N_6O_2$: C, 64.16; H, 4.85; N, 22.45. Found: C, 63.96; H, 4.92; N, 22.30.

4.2.11. 2-[2,6-Bis(benzylamino)-5-nitropyrimidin-4-yl]-3-phenylpropionitrile (15). Compound **14** (3.7 g, 10 mmol) was dissolved in dimethyl sulfoxide (30 mL), tributylamine (5 mL) and then benzyl bromide (2.6 g, 15 mmol) were added, and the reaction mixture was stirred overnight. Methanol (5 mL) was added, the reaction mixture was taken into ethyl acetate and washed with sodium hydrogencarbonate and brine. Chromatography on a silica gel column (chloroform) followed by crystallization (petroleum ether–ethyl acetate 3:1) afforded compound **15** (3.3 g, 71%, yellow crystals, mp 187–188 °C) as a mixture of 2 tautomers (4.3:1). MS (EI) *m*/*z* (rel. intensity): 464 (32, M), 447 (11, M−OH), 358 (6, M−BnNH$_2$), 341 (12, M−BnNH$_2$-OH), 253 (11, M−2BnNH$_2$+H), 106 (8, BnNH$_2$), 91 (100, Bn). ^{1}H NMR (500 MHz, DMSO-d_6, *minor tautomer in italic*): 9.41 (t, 1H, $J = 6.0$, NH), *9.15 (t, 1H,* $J = 6.0$, *NH*), 8.92 (t, 1H, $J = 6.4$, NH), *8.68 (t, 1H,* $J = 6.4$, *NH*), 7.40–7.10 (m, 15H, Ph), *7.40–7.10 (m, 15H, Ph)*, 5.10 (dd, 1H, $J = 10.6$, 4.4, CHCN), *5.09 (dd, 1H,* $J = 10.3$, *4.5, CHCN), 4.69 (d, 2H,* $J = 6.0$, *N–CH$_2$–Ph*), 4.68 (d, 2H, $J = 6.0$, N–C*H*$_2$–Ph), *4.56 (d, 2H,* $J = 6.4$, *N–CH$_2$–Ph*), 4.45 (d, 2H, $J = 6.4$, N–C*H*$_2$–Ph), 3.33 (dd, 1H, $J = 13.4$, 4.4, C–C*H*$_2$–Ph), *3.26 (dd, 1H,* $J = 13.4$, *4.5, CCH$_2$–Ph)*, 2.99 (dd, 1H, $J = 13.4$, 10.6, C–C*H*$_2$–Ph), *2.95 (dd, 1H,* $J = 13.4$, *10.3, C–CH$_2$–Ph)*. ^{13}C NMR (125.7 MHz, DMSO-d_6, *minor tautomer in italic*): 163.37 (C-4), *163.23 (C-4)*, 159.02 (C-6), *158.96 (C-6), 156.66 (C-2)*, 156.57 (C-2), *139.88 (Ph)*, 139.39 (Ph), 139.28 (Ph), *139.21 (Ph)*, 137.57 (Ph), *137.47 (Ph)*, 129.49 (2C, Ph), 128.99 (2C, Ph), 128.73 (2C, Ph), 128.72 (2C, Ph), 127.88 (2C, Ph), 127.71 (2C, Ph), *119.82 (C-5)*, 119.79 (C-5), *119.39 (CN)*, 119.37 (CN), *44.60 (N–CH_2–Ph)*, 44.48 (N–CH_2–Ph), *44.43 (N–CH_2–Ph)*, 44.32 (N–CH_2–Ph), *41.16 (C–CN)*, 40.89 (*C*–CN), 38.03 (C–CH_2–Ph), *37.96 (C–CH_2–Ph)*. IR ($CHCl_3$): 3430, 3370, 3022, 2250, 1593, 1583, 1571, 1550, 1509 cm^{-1}. UV/vis (MeOH): 369 ($\varepsilon = 8700$), 268 ($\varepsilon = 4300$). Anal. Calcd for $C_{27}H_{24}N_6O_2$: C, 69.81; H, 5.21; N, 18.09. Found: C, 70.04; H, 5.35; N, 17.88.

4.2.12. 2-Benzyl-2-[2,6-bis(dibenzylamino)-5-nitropyrimidin-4-yl]-3-phenylpropionitrile (16). Compound **15** (930 mg, 2 mmol) was dissolved in dimethyl sulfoxide (6 mL), sodium hydride (60% dispersion in mineral oil, 100 mg, 2.5 mmol) and then benzyl bromide (430 mg, 2.5 mmol) was added and the reaction mixture was stirred overnight. Methanol (2 mL) was added, the reaction mixture was taken into ethyl acetate and washed with sodium hydrogen carbonate and brine. Chromatography on a silica gel column (petroleum ether–ethyl acetate 14:1) afforded compound **16** as yellow amorphous solid (380 mg, 26%; When 3 equiv of BnBr and NaH were used the yield amounted to 1.2 g, 82%). MS (EI) *m/z* (rel. intensity): 734 (1.1, M), 717 (0.5, M−OH), 704 (1.4, M−NO), 688 (1.1, M−NO_2), 643 (8, M−Bn), 609 (7), 432 (4), 427 (6), 91 (100, Bn). MS (FAB) *m/z* (rel. intensity): 735 (10, M+H). ^{1}H NMR (500 MHz, DMSO-d_6): 7.35–7.05 (m, 25H, Ph), 4.59 s (2H, CH_2–Ph), 4.53 (s, 2H, CH_2–Ph), 4.48 (s, 4H, CH_2–Ph), 3.61 (d, 2H, *J* = 13.7, CH_2-Ph), 3.23 (d, 2H, *J* = 13.7, CH_2–Ph). ^{13}C NMR (125.7 MHz, DMSO-d_6): 158.84 (C-6), 158.55 (C-4), 156.16 (C-2), 137.92 (Ph), 137.71 (Ph), 136.89 (2C, Ph), 135.51 (2C, Ph), 130.81 (2C, Ph), 128.66 (2C, Ph), 128.62 (4C, Ph), 128.50 (2C, Ph), 128.25 (4C, Ph), 127.88 (2C, Ph), 127.46 (2C, Ph), 127.40 (2C, Ph), 127.39 (4C, Ph), 127.23 (4C, Ph), 127.10 (2C, Ph), 125.14 (C-5), 119.59 (CN), 53.37 (4C, CH_2–Ph), 49.93 (*C*–CN), 42.84 (CH_2–Ph), 39.53 (CH_2–Ph). IR ($CHCl_3$): 3032, 3020, 2240, 1546, 1523, 1496, 1454, 1328, 1250, 1029, 971 cm^{-1}. UV/vis (MeOH): 302 (9200), 245 (23,800). Anal. Calcd for $C_{48}H_{42}N_6O_2$: C, 78.45; H, 7.76; N, 11.44. Found: C, 78.26; H, 5.98; N, 11.23.

4.2.13. *N*^{2},*N*^{4}-Dibenzyl-5*H*-pyrrolo[3,2-d]pyrimidine-2,4-diamine (17) hydrochloride. Compound **14** (750 mg, 2 mmol) in methanol (100 mL) acidified with methanolic hydrogen chloride (1 M, 5 mL) was hydrogenated under slight overpressure in the presence of Pd/C catalyst (10 wt %, 40 mg) overnight. The catalyst was filtered off through a Celite pad and the filtrate evaporated. Chromatography on a silica gel column (chloroform–methanol, 97:3) followed by crystallization (ethyl acetate–methanol, 6:1) afforded hydrochloride of compound **17** (380 mg, 52%) mp 206–208 °C. MS (EI) *m/z* (rel. intensity): 329, 238 (M−Bn), 224 (M−BnNH+H), 106 (34, BnNH), 91 (100, Bn). MS (FAB) *m/z* (rel. intensity): 330 (100, M+H). ^{1}H NMR (500 MHz, DMSO-d_6): 12.41 (br s, 1H, NH), 12.14 (br s, 1H, NH), 9.66 (br s, 1H, NH), 8.24 (br s, 1H, NH), 7.28 (m, 10H, Ph), 7.49 (t, 1H, *J* = 2.8, 3.1, H-6), 6.21 (t, 1H, *J* = 2.8, 2.1, H-7), 4.70 (d, 2H, *J* = 5.9, CH_2Ph), 4.58 (d, *J* = 6.1, CH_2Ph). ^{13}C NMR (125.7 MHz, DMSO-d_6): 151.95 (C-2), 151.29 (C-4), 139.09 (Ph), 138.41 (Ph), 134.43 (C-7a), 128.99 (C-6), 128.63 (2C, Ph), 128.55 (2C, Ph), 127.89 (2C, Ph), 127.36 (3C, Ph), 127.16, 108.46 (C-4a), 95.66 (C-7), 44.50 (NCH_2), 43.66 (NCH_2). IR (KBr): 3254, 3110, 1649, 1619, 1570, 1478, 1391, 1352, 1169, 766, 739, 578 cm^{-1}. UV (MeOH): 293 ($\varepsilon = 15,600$), 239 ($\varepsilon = 23,800$). Anal. Calcd for $C_{20}H_{20}ClN_5$ (365.9): C, 65.66; H, 5.51; Cl, 9.69; N, 19.14. Found: C, 65.34; H, 5.60; Cl, 9.70; N, 19.19.

4.2.14. 7,*N*^{2},*N*^{4}-Tribenzyl-5*H*-pyrrolo[3,2-*d*]pyrimidine-2,4-diamine (18) hydrochloride. Compound **15** (930 mg, 2 mmol) in methanol (100 mL) acidified with methanolic hydrogen chloride (1 M, 5 mL) was hydrogenated under slight overpressure in the presence of Pd/C catalyst (10 wt %, 40 mg) overnight. The catalyst was filtered off through a Celite pad and the filtrate evaporated. Chromatography on a silica gel column (chloroform–methanol, 98:2) followed by crystallization (ethyl acetate–methanol, 9:1) afforded hydrochloride of compound **18** (565 mg, 62%), mp 236–237 °C. MS (EI) *m/z* (rel. intensity): 419 (100, M), 328 (31, M−Bn), 314 (30, M−$BnNH_2$+H), 91 (92, Bn). ^{1}H NMR (500 MHz, DMSO-d_6): 12.44 (s, 1H, NH), 11.68 (s, 1H, NH), 9.38 (t, 1H, *J* = 6.0, NH), 7.83 (t, 1H, *J* = 6.4), 7.40–7.10 (m, 15H, Ph), 7.27 (s, 1H, H-6), 4.70 (d, 2H, *J* = 6.0, CH_2–Ph), 4.61 (d, 2H, *J* = 6.4, CH_2–Ph), 3.93 (s, 2H, CH_2–Ph). ^{13}C NMR (125.7 MHz, DMSO-d_6): 152.12 (C-4), 151.27 (C-2), 141.99 (Ph), 140.69 (Ph), 139.12 (Ph), 138.40 (Ph), 132.63 (C-7a), 128.60 (2C, Ph), 128.54 (4C, Ph), 128.50 (2C, Ph), 128.43 (2C, Ph), 128.32 (2C, Ph), 127.85 (2C, Ph), 127.75 (C-6), 127.39 (2C, Ph), 127.33 (Ph), 127.15 (Ph), 126.15 (Ph), 125.74 (Ph), 108.36 (C-4a), 109.01 (C-7), 44.73 (N–C_2–Ph), 44.53 (N–CH_2–Ph), 29.07 (C–CH_2–Ph). IR (KBr): 3248, 3150, 3106, 3027, 1648, 1616, 1569, 1469, 1454, 1394, 733, 696 cm^{-1}. UV (MeOH): 296 ($\varepsilon = 19,000$), 242 ($\varepsilon = 23,700$). Anal. Calcd for $C_{27}H_{26}ClN_5$: C, 71.12; H, 5.75; Cl, 7.77; N, 15.36. Found: C, 70.93; H, 5.85; Cl, 8.03; N, 15.19.

4.2.15. 7,7,*N*^{2},*N*^{2},*N*^{4},*N*^{4}-Hexabenzyl-7*H*-pyrrolo[3,2-*d*]-pyrimidine-2,4,6-triamine (19). Compound **16** (1.5 g, 2 mmol) in methanol (100 mL) acidified with methanolic hydrogen chloride (1 M, 5 mL) was hydrogenated under slight overpressure in the presence of Pd/C catalyst (10 wt %, 40 mg) overnight. The catalyst was filtered off through a Celite pad and the filtrate evaporated. Chromatography on a silica gel column (chloroform) afforded compound **19** (780 mg, 55%) as yellowish foam. MS (EI) *m/z* (rel. intensity):704 (58, M), 613 (49, M−Bn), 523 (6, M−2Bn+H), 521 (6, M−2Bn−H), 431 (100, M−3Bn), 338 (5, M−4Bn−2H), 91 (74, Bn). ^{1}H NMR (500 MHz, DMSO-d_6): 8.02–7.52 (m, 10H, Ph), 7.35–7.05 (m, 20H, Ph), 6.74 (s, 2H, NH_2), 4.81 (s, 4H, N–CH_2–Ph), 4.50 (s, 4H, N–CH_2–Ph), 3.20 (s, 4H, C–CH_2–Ph). ^{13}C NMR (125.7 MHz, DMSO-d_6): 168.72 (C-7a), 165.58 (C-6), 157.01 (C-4), 150.84 (C-2), 140.11 (Ph), 139.15 (Ph), 136.82 (4C, Ph), 129.77–127.42 (Ph, 24C), 124.45 (C-4a), 59.53 (C-7), 49.93 (4C, N–*C*H$_2$–Ph), 41.58 (2C, C-*C*H$_2$–Ph). IR (CHCl$_3$): 3401, 3011, 2916, 1620, 1587, 1566, 1495, 1473, 1452, 1416, 1338, 1264, 972, 700 cm^{-1}. UV/vis (MeOH): 354 ($\varepsilon = 5800$), 297 ($\varepsilon = 16,250$), 231 ($\varepsilon = 21,340$). Anal. Calcd for $C_{48}H_{44}N_6$: C, 81.79; H, 6.29; N, 11.92. Found: C, 81.53; H, 6.42; N, 11.76.

4.2.16. *N*-(4-Acetylamino-6-methyl-5-nitropyrimidin-2-yl)acetamide (20). Compound **1** (1.7 g, 10 mmol) in a mixture of acetic anhydride and acetic acid (1:1, 40 mL) was heated to reflux for 3 h; then the volatiles were evaporated. Chromatography on a silica gel column (chloroform–methanol, 98:2) followed by crystallization (ethyl acetate) afforded compound **20** (2.0 g, 79%) as white crystals, mp 160–161 °C. MS (EI) m/z (rel. intensity): 253 (4, M), 211 (22, M−Ac+H), 207 (100, M−NO$_2$), 169 (29, M−2Ac+2H), 165 (44, M−NO$_2$–Ac+H), 152 (43, M−2Ac–Me), 43 (76, Ac). ^{1}H NMR (500 MHz, DMSO-d_6): 11.13 (s, 1H, NH), 10.90 (s, 1H, NH), 2.52 (s, 3H, Me), 2.22 (s, 3H, CH$_3$ CO), 2.11 (s, 3H, CH$_3$CO). ^{13}C NMR (125.7 MHz, DMSO-d_6): 169.91 (CO), 169.49 (CO), 163.72 (C-6), 156.40 (C-4), 151.43 (C-2), 132.67 (C-5), 25.08 (*C*H$_3$CO), 23.51 (*C*H$_3$CO), 22.41 (Me). IR (CHCl$_3$): 3389, 3260, 3183, 3020, 1731, 1714, 1686, 1564, 1373, 1304 cm^{-1}. UV (MeOH): 275 (sh, $\varepsilon = 8100$), 242 ($\varepsilon = 22,260$). Anal. Calcd for $C_9H_{11}N_5O_4$: C, 42.69; H, 4.38; N, 27.66. Found: C, 42.66; H, 4.55; N, 27.94.

4.2.17. *N*-(4-Benzoylamino-6-methyl-5-nitropyrimidin-2-yl)benzamide (21). Compound **1** (1.7 g, 10 mmol) was melted with benzoic anhydride (9.0 g, 40 mmol) at 100 °C for 3 h. The reaction mixture was taken into ethyl acetate and washed with sodium hydrogen carbonate and brine. Chromatography on a silica gel column (chloroform) followed by crystallization (ethyl acetate) afforded compound **21** (3.2 g, 85%) as white crystals, mp 131–132 °C.MS (EI) m/z (rel. intensity): 377 (0.2, M), 361 (0.3), 348 (4, M−NO+H), 331 (42, M−NO$_2$), 105 (100, Bz), 77 (47, Ph). ^{1}H NMR (500 MHz, DMSO-d_6): 11.76 (s, 1H, NH), 11.46 (s, 1H, NH), 8.02–7.52 (m, 10H, Ph), 2.63 (s, 3H, Me). ^{13}C NMR (125.7 MHz, DMSO-d_6): 166.84 (CO), 165.94 (CO), 163.84 (C-6), 157.29 (C-4), 152.72 (C-2), 134.13 (C-5), 133.85 (Ph), 133.32 (Ph), 132.73 (Ph), 132.22 (Ph), 128.85 (2C, Ph), 128.75 (2C, Ph), 128.65 (4C, Ph), 22.40 (Me). IR (CHCl$_3$): 3426, 1713, 1575, 1482, 1432, 1356, 1232, 842, 706 cm^{-1}. UV (MeOH): 260 ($\varepsilon = 37,000$). Anal. Calcd for $C_{19}H_{15}N_5O_4$: C, 60.48; H, 4.01; N, 18.56. Found: C, 60.22; H, 4.09; N, 18.43.

4.2.18. *N*-(4-Acetylamino-6-dibromomethyl-5-nitropyrimidin-2-yl)acetamide (22). Compound **20** (2.5 g, 10 mmol) and sodium acetate (1.6 g, 20 mmol) were added to a solution of bromine (3.2 g, 20 mmol) in acetic acid (100 mL)and the reaction mixture was heated to 65 °C for 20 min. The solvent was evaporated to a small volume, taken into ethyl acetate and washed with water and brine. Chromatography on a silica gel column (chloroform) followed by crystallization (diethyl ether–ethyl acetate 8:1) afforded compound **22** (3.0 g, 73%) as white crystals, mp 178–180 °C. MS (EI) m/z (rel. intensity): 413 (2), 411 (4), 409 (2, M), 367 (54), 365 (100), 363 (52, M−NO$_2$), 325 (17), 323 (24), 321 (12, M−NO$_2$–Ac), 287 (14), 285 (15, M−Br), 244 (14), 242 (14, M−Br-Ac), 220 (16), 218 (18), 167 (24), 122 (32), 81 (35), 79 (33), 68 (48). ^{1}H NMR (500 MHz, DMSO-d_6): 11.42 (s, 1H, NH), 11.18 (s, 1H, NH), 7.30 (s, 1H, CHBr$_2$), 2.32 (s, 3H, *CH*$_3$ CO), 2.14 (s, 3H, *CH*$_3$ CO). ^{13}C NMR (125.7 MHz, DMSO-d_6): 170.27 (CO), 169.97 (CO), 159.76 (C-6), 157.25 (C-4), 152.76 (C-2), 127.31 (C-5), 36.93 (CHBr$_2$), 25.47 (C_3 CO), 23.56 (*C*H$_3$ CO). IR (KBr): 3447, 3291, 3198, 1679, 1592, 1543, 1293, 1281 cm^{-1}. UV/vis (MeOH): 356 ($\varepsilon = 9780$), 264 ($\varepsilon = 9850$), 229 ($\varepsilon = 21,450$). Anal. Calcd for $C_9H_9Br_2N_5O_4$: C, 26.30; H, 2.21; Br, 38.88; N, 17.04. Found: C, 26.02; H, 2.43; Br, 39.12; N, 16.84.

4.2.19. *N*-(4-Benzoylamino-6-dibromomethyl-5-nitropyrimidin-2-yl)benzamide (23). Compound **21** (2.3 g, 6 mmol) and sodium acetate (980 mg, 12 mmol) were added to a solution of bromine (1.9 g, 12 mmol) in acetic acid (60 mL) and the reaction mixture was heated to 65 °C for 20 min. The solvent was evaporated to a small volume, taken into ethyl acetate and washed with water and brine. Chromatography on a silica gel column (chloroform) followed by crystallization (diethylether–ethyl acetate 9:1) afforded compound **23** (2.6 g, 81%) as white crystals, mp 115–117 °C. MS (EI) m/z (rel. intensity): 491 (52), 489 (92), 487 (61, M−NO$_2$), 411 (42), 409 (43, M−NO$_2$–Br), 226 (100, M−NO$_2$–2Br–Bz+2H). ^{1}H NMR (500 MHz, DMSO-d_6): 12.07 (s, 1H, NH), 11.78 (s, 1H, NH), 8.02–7.52 (m, 10H, Ph), 7.38 (s, 1H, CHBr$_2$). ^{13}C NMR (125.7 MHz, DMSO-d_6): 167.15 (CO), 166.43 (CO), 159.92 (C-6), 158.34 (C-4), 154.06 (C-2), 133.85 (Ph), 133.32 (Ph), 132.73 (Ph), 132.22 (Ph), 128.85 (2C, Ph), 128.75 (2C, Ph), 128.75 (C-5), 128.65 (4C, Ph), 36.84 (CHBr$_2$). IR (CHCl$_3$): 3470, 3417, 1711, 1571, 1545, 1480, 1390, 1349, 1288, 1004, 844, 707, 597 cm^{-1}. UV (MeOH): 260 ($\varepsilon = 25,000$). Anal. Calcd for $C_{19}H_{13}Br_2N_5O_4$: C, 42.64; H, 2.45; Br, 29.86; N, 13.09. Found: C, 42.41; H, 2.56; Br, 29.62; N, 12.92.

4.2.20. *N*-[6-(1,1-Dibenzyl-1-cyanomethyl)-2-benzoylamino-5-nitropyrimidin-4-yl]benzamide (24). To a suspension of potassium cyanide (1.0 g, 16 mmol) in dimethyl sulfoxide (40 mL) cooled to 0 °C compound **23** (1.7 g, 3.2 mmol) was added portionwise within 15 min and the reaction mixture was left at room temperature for additional 20 min. Benzyl bromide (3.4 g, 20 mmol) was added and the reaction mixture was stirred over night. The reaction mixture was taken into ethyl acetate and washed with brine. Chromatography on a silica gel column (chloroform) followed by crystallization (petroleum ether–ethyl acetate 3:1) afforded compound **24** (150 mg, 9%) as white crystals, mp 264–265 °C. MS (FAB) m/z (rel. intensity): 583 (24, M+H), 355 (100). MS (EI) m/z (rel. intensity): 446 (21, M−Bn−NO$_2$+H), the molecular peak does not manifest. ^{1}H NMR (500 MHz, DMSO-d_6): 11.70 (s, 1H, NH), 11.61 (s, 1H, NH), 8.02–7.52 (m, 10H, Ph), 7.35–7.30 (m, 5H, Ph), 3.92 (d, 2H, $J = 13.4$, CH_2–Ph), 3.23 (d, 2H, $J = 13.4$, CH_2–Ph). ^{13}C NMR (125.7 MHz, DMSO-d_6): 166.87 (CO), 166.44 (CO), 158.40 (C-4), 156.51 (C-6), 154.85 (C-2), 135.51 (2C, Ph), 132.08 (C-5), 133.85 (Ph), 133.32 (Ph), 132.73 (Ph), 132.22 (Ph), 130.81 (4C, Ph), 128.85 (2C, Ph), 128.75 (2C, Ph), 128.65 (4C, Ph), 128.25 (4C, Ph), 127.46 (2C, Ph), 117.70 (CN), 51.06 (*C*–CN), 43.22 (CH$_2$–Ph), 39.86 (C_2–Ph). IR (KBr): 3385, 3301, 1729, 1685, 1569, 1522, 1455, 1234, 701 cm^{-1}. UV (MeOH): 260 ($\varepsilon = 30400$). Anal. Calcd for $C_{34}H_{26}N_6O_4$: C, 70.09; H, 4.50; N, 14.42. Found: C, 69.83; H, 4.20; N, 14.35.

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