Synthesis and Modeling Study of Some Potential Pyrimidine Derivatives as HIV Inhibitors

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A new series of 2-amino-6-((4-aryldiazenyl)benzyloxy)-4-chloropyrimidine derivatives **4** – **13** and 2,6-diamino-5-arylazo-4-chloro-pyrimidine analogs **15** – **20** were synthesized from the pyrimidine scaffolds **3** and **14**, respectively, *via* diazotization with various amines. Nucleophilic displacement at the 2,4-diamino-5-arylazo-6-chloro-pyrimidine **16** by different amines afforded the 4-alkylamino analogs **21** – **27**. All new compounds were evaluated for their *in vitro* anti-HIV activity in MT-4 cells as non-nucleoside reverse transcriptase inhibitors on the basis of our previous work. Screening results indicated that **10** and **11** were found to be the only compounds in the series inhibiting HIV-1 replication in cell cultures with EC_{50} of > 1.23 and $> 2.92\ \mu g\ mL^{-1}$ of a CC_{50} of 12.30 and $17.52\ \mu g\ mL^{-1}$, resulting in a selectivity index of 10 and 6, respectively. In addition, preliminary structure-activity relationships and molecular modeling of these new analogs are detailed in this manuscript.

Key words: Anti-HIV Activity, Diazotization, NNRTIs, Pyrimidines, Molecular Modeling Study

Introduction

Pyrimidines are an important class of organic compounds, some of which show significant biological activity such as antitumor [1 – 6], antimicrobial [7 – 10], and antihypertensive [11] agents, in addition to their cardiovascular [12, 13] and diuretic [14, 15] properties. Furthermore, pyrimidines are compounds with *in vitro* biological activity against a wide spectrum of unrelated viruses, such as poliovirus [16] herpes [17] and HI [18 – 20]. For the latter, two diarylpyrimidines (DAPY), rilpivirine (**1**) [21] and etravirine (**2**) [22, 23], have been classified as non-nucleoside reverse transcriptase inhibitors (Fig. 1). Bacimethrin (4-amino-5-(hydroxymethyl)-2-methoxypyrimidine), a pyrimidine antibiotic, is active against several staphylococcal bacteria [24]. Gemcitabine (**3**), a pyrimidine antimetabolite, is an approved drug in the U. S. for pancreatic cancer and also in combination for certain lung cancer patients [25], while 2,4-diamino-N^4-6-diarylpyrimidines were identified to block the proliferation of tumor cell lines *in vivo*, especially duodenum cancer [26]. Recently, Kim *et al.* [27] have reported some novel pyrimidine derivatives as potent acid pump antagonists (APAs). Jian *et al.* [28] have reviewed the biological and medicinal significance of pyrimidines extensively.

In continuation of our ongoing work on the synthesis of new anti-HIV agents and our recent antiviral data on new pyrimidine derivatives [29, 30], we report here the synthesis of new series of pyrimidines having arylazo residues, and the evaluation of their

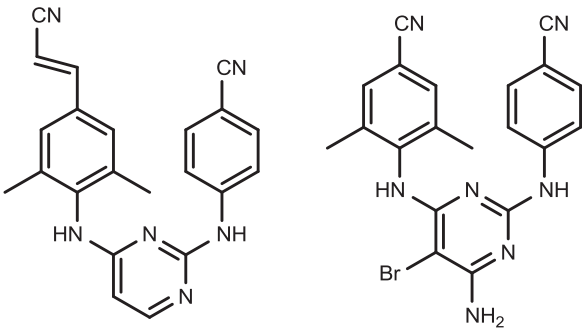
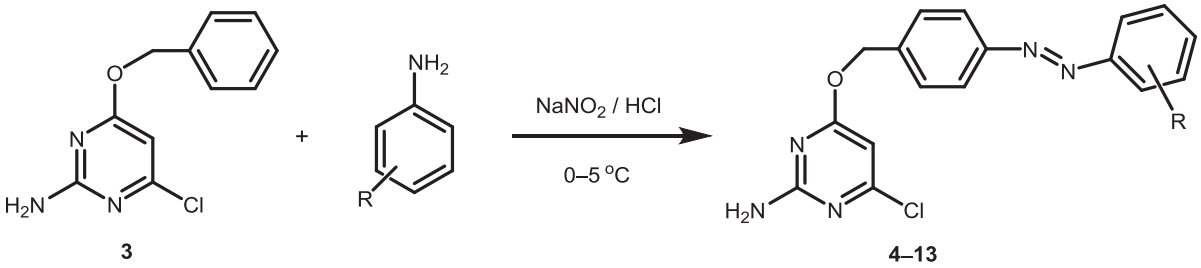


Fig. 1. Chemical sructures of rilpivirine (**1**) and etravirine (**2**).



Compound	R	Compound	R
4	H	**9**	4-CH_2OH
5	4-Me	**10**	3,4-Cl_2
6	4-Cl	**11**	4-Cl,3-I
7	4- Br	**12**	4-CO_2Me
8	4-NO_2	**13**	4-NHCOMe

Scheme 1. Synthesis of 2-amino-((4-aryldiazenyl)benzyloxy)-4-chloropyrimidine derivatives **4** – **13**.

anti-HIV activity together with a SAR and modeling study.

Results and Discussion

2-Amino-4-benzyloxy-6-chloropyrimidine (**3**) has been selected as a key intermediate for the synthesis of new azo-pyrimidine derivatives, aiming at the evaluation of their anti-HIV activity. Thus, treatment of **3** with various substituted anilines in the presence of $NaNO_2$ and HCl first at 0 – 5 °C, then at ambient temperature for 15 h, afforded, after purification, mainly the azoaryl-pyrimidine analogs **4** – **13** (65 – 83 %) (Scheme 1).

The structures of **4** – **13** were assigned on the basis of their ^{1}H, ^{13}C NMR and mass spectra. The ^{1}H NMR of **4** – **13** showed similar patterns for the aromatic and pyrimidine protons and carbon atoms, where 5-H appeared as singlet in the region $\delta = 6.54 - 6.74$ ppm. The singlets in the region $\delta = 5.31 - 5.51$ ppm were attributed to the methylene group of the benzyl residue. In the ^{13}C NMR spectra of **4** – **13**, the resonances at $\delta = 172.0 - 174.3$ ppm were assigned to C-4, while the resonances at $\delta = 159.0 - 162.1$ ppm were attributed to C-2 of the pyrimidine ring. The signals of C-6 and C-5 appeared at $\delta = 161.8 - 162.8$ and 99.3 – 101.0 ppm, respectively. The CH_2 signal appeared at $\delta = 50.4 - 51.6$ ppm. The other carbon atoms of the aromatic substituents were fully assigned (see Experimental Section). The proton and carbon systems of the aromatic ring are further identified from the DFQ-COSY spectra [31]. Compound **9** was selected for further NMR experiments. The gradient HMBC [32] NMR spectrum of **9** showed two $^2J_{C,H}$ couplings between the methylene protons of the benzyl group at $\delta = 5.33$ ppm and C-4″ of the aromatic ring at $\delta = 144.4$ ppm as well as C-1′ of the aromatic residue at $\delta = 137.4$ ppm. Additionally, a $^3J_{C,H}$ coupling between the same methylene protons at $\delta = 5.33$ ppm and C-4 of the pyrimidine ring at $\delta = 172.4$ ppm was observed (Fig. 2).

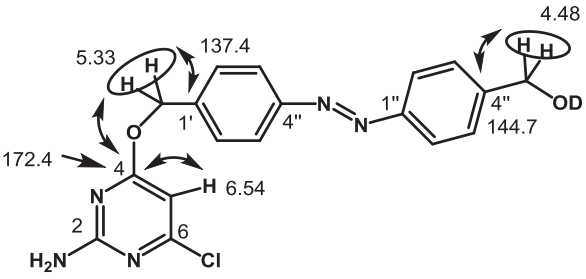
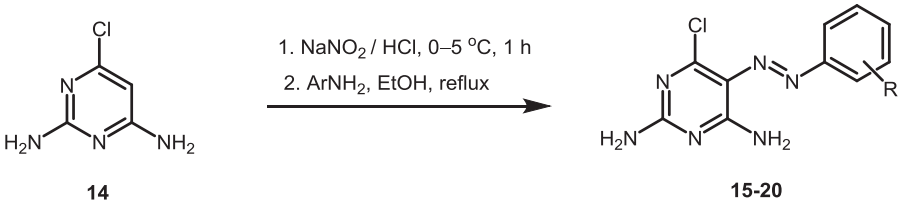


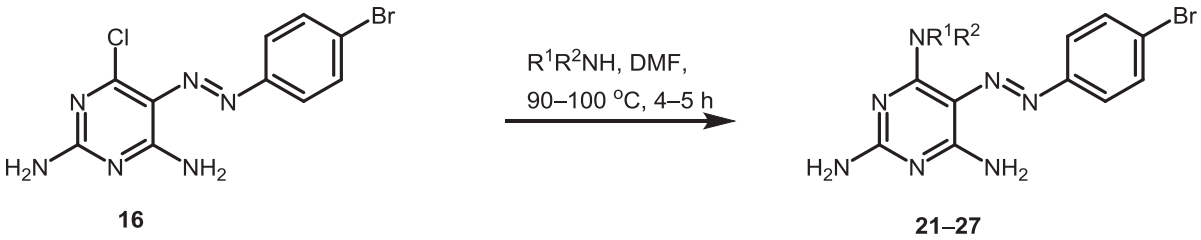
Fig. 2. ^{1}H and ^{13}C NMR chemical shifts (δ in ppm) and $J_{C,H}$ correlations in the HMBC NMR spectrum of **9**.



14 **15-20**

Compound	R	Yield (%)
15	4-Cl	80
16	4-Br	58
17	4-NO_2	36
18	4-CO_2Me	87
19	4-NHCOMe	76
20	4-NO_2	61

Scheme 2. Synthesis of 2,6-diamino-5-(arylazo)-4-chloropyrimidine derivatives **15** – **20**.



16 **21–27**

Compound	R^1	R^2	Compound	R^1	R^2
21	H	Me	**25**	H	$(CH_2)_5CH_3$
22	H	Pr	**26**	H	CH_2CH_2OH
23	H	Bu	**27**	H	$CHCH_3CH_2OH$
24	H	$(CH_2)_4CH_3$			

Scheme 3. Synthesis of 4-alkylamino-2,6-diamino-5-(*p*-bromophenyldiazenyl)pyrimidine derivatives **21** – **27**.

Our work was modified by selecting **14** as a precursor for the synthesis of new 5-arylazopyrimidine derivatives to examine their antiviral activity in comparison to the azoaryl analogs **4** – **13**. Thus, diazotization of **14**, following the same method as described above, by using various substituted anilines gave the desired azoaryl analogs **15** – **20** (Scheme 2). The structures of **4** – **13** were determined from their ^{1}H, ^{13}C NMR and mass spectra, since they showed similar patterns of aromatic and pyrimidine protons (see Experimental Section). In the ^{13}C NMR spectra of **4** – **13**, C-2 of the pyrimidine ring resonated at $\delta = 165.2 - 166.1$ ppm, while C-4, C-5 and C-6 resonated at $\delta = 131.3 - 136.5$, 119.2 – 121.4 and 155.0 – 156.7 ppm, respectively.

Next, the derivative **16** was subjected to a nucleophilic displacement of the chlorine atom by treatment with various amines at 90 – 100 °C leading to new 4-alkylamino-pyrimidine derivatives **21** – **27** (88 – 64 %) (Scheme 3). The structures of **21** – **27** were established by ^{1}H, ^{13}C NMR and mass spectral data. In the ^{13}C NMR spectra of **21** – **27**, C-6 and C-4

Table 1. *In-vitro* anti-HIV-1[a] and HIV-2[b] activity of the new pyrimidine derivatives **4** – **13** and **16** – **27**.

Compound	Virus strain	EC_{50} ($\mu g\,mL^{-1}$)[c]	CC_{50} ($\mu g\,mL^{-1}$)[d]	SI[e]
4	III_B	> 6.93	6.93	< 1
	ROD	> 6.93	6.93	< 1
5	III_B	> 125.0	125.0	< 1
	ROD	> 125.0	125.0	< 1
6	III_B	> 125.0	125.0	< 1
	ROD	> 125.0	125.0	< 1
7	III_B	> 92.68	92.68	< 1
	ROD	> 92.68	92.68	< 1
8	III_B	> 125.0	125.0	< 1
	ROD	> 125.0	125.0	< 1
9	III_B	> 125.0	125.0	< 1
	ROD	> 125.0	125.0	< 1
10	III_B	> 1.23	12.30	10
	ROD	> 1.23	1.23	< 1
11	III_B	> 2.92	17.52	< 6
	ROD	> 2.92	2.92	< 1
12	III_B	> 59.30	59.30	< 1
	ROD	> 59.30	59.30	< 1
13	III_B	> 43.75	43.75	< 1
	ROD	> 43.75	43.75	< 1
16	III_B	> 59.78	59.78	< 1
	ROD	> 59.78	59.78	< 1
17	III_B	> 13.48	13.48	< 1
	ROD	> 13.48	13.48	< 1
18	III_B	> 18.23	18.23	< 1
	ROD	> 18.23	18.23	< 1
19	III_B	> 16.36	16.36	< 1
	ROD	> 16.36	16.36	< 1
20	III_B	> 5.31	5.31	< 1
	ROD	> 5.31	5.31	< 1
21	III_B	> 12.78	12.78	< 1
	ROD	> 12.78	12.78	< 1
22	III_B	> 8.28	8.28	< 1
	ROD	> 8.28	8.28	< 1
23	III_B	> 5.57	5.57	< 1
	ROD	> 5.57	5.57	< 1
24	III_B	> 4.79	4.79	< 1
	ROD	> 4.79	4.79	< 1
25	III_B	> 4.10	4.10	< 1
	ROD	> 4.10	4.10	< 1
26	III_B	> 94.20	94.20	< 1
	ROD	> 94.20	94.20	< 1
27	III_B	> 6.80	6.80	< 1
	ROD	> 6.80	6.80	< 1
AZT	III_B	0.0022	> 25	> 11 363
	ROD	0.00094	> 25	> 26 596
Nevirapine	III_B	0.050	> 4.00	> 80
	ROD	> 4.00	> 4.00	< 1

[a] Anti-HIV-1 activity measured with strain III_B; [b] anti-HIV-2 activity measured with strain ROD; [c] compound concentration required to achieve 50 % protection of MT-4 cells from the HIV-1 and 2-induced cytopathogenic effect; [d] compound concentration that reduces the viability of mock-infected MT-4 cells by 50 %; [e] SI: selectivity index (CC_{50}/EC_{50}).

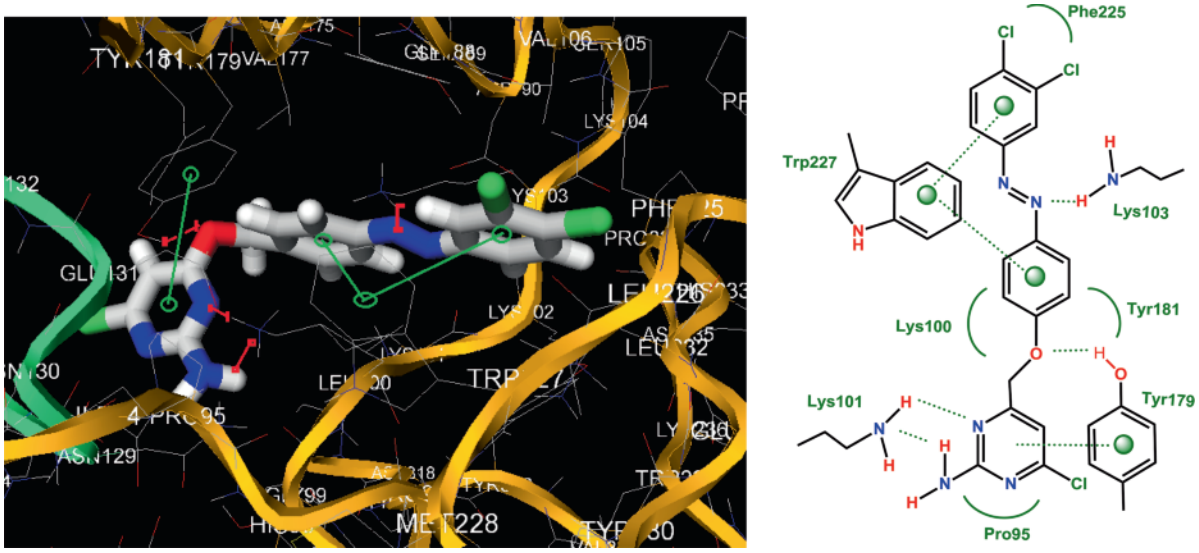


Fig. 3. (color online). Docked conformation of **27** showing four hydrogen bonds: Lys101 with NH_2 and N^3 of the pyrimidine ring, Tyr179 with the oxygen atom of the benzyl group and Lys103 with the N=N group. It also exhibits hydrophobic interactions involving the phenyl moieties Tyr179 and Trp227 of reverse transcriptase (RT) enzyme residues.

of the pyrimidine scaffold resonated in the region $\delta = 163.2 - 164.0$ ppm, while C-5 and C-6 appeared in the regions $\delta = 104.7 - 110.6$ and $152.0 - 157.7$ ppm, respectively (see Experimental Section). Moreover, all the synthesized compounds were further identified by a ^{1}H, ^{13}C HSQC [33] spectroscopic study.

In-vitro anti-HIV activity

Compounds **5**–**7** and **12**–**17** were tested for their *in vitro* anti-HIV-1 (strain III_B) and HIV-2 (strain ROD) activity in human T-lymphocyte (MT-4) cells based on an MTT assay [34]. The results are summarized in Table 1, in which the data for nevirapine (BOE/BIRG587) [35] and azidothymidine (DDN/AZT) [36] were included for comparison. Compounds **10** and **11** were found to be the only compounds in the series inhibiting HIV-1 replication in cell cultures with EC_{50} of $> 1.23\,\mu g\,mL^{-1}$ and > 2.92 of a CC_{50} of 12.30 and $17.52\,\mu g\,mL^{-1}$, resulting in a selectivity index of 10 and 6, respectively.

From the SAR analysis, we found that the halogen atom on the aromatic ring, *e. g.* in **10** and **11**, were well tolerated in the hydrophobic region of HIV RT and then showed higher activity than those of the derivatives with other substituents of the same series of Scheme 1.

Molecular modeling analysis

Our molecular docking analysis of the new analogs is based on the modeling studies which were performed to understand the binding mode of these analogs with the HIV-RT binding pocket (NNIBP) (PDB code: 3DLG, [37]). The molecular docking was performed using SYBYL-X 1.1, and the results were visualized with PYMOL [38].

The prospective ligands were ranked according to the highest binding energy of the best conformers. Thus, the binding energy score for the **4**–**13** and **16**–**27** series ranged from -6.97 to $-10.02\,kcal\,mol^{-1}$ (Table 2), indicating selectivity and potency profiles of these derivatives to bind the active site of HIV-RT pocket, especially those carrying haloaryl residues (*e. g.* **10**). Compound **10** has been selected to show its binding to the enzyme pocket (Fig. 3). As shown in Fig. 3, the aromatic rings of **10** fitted into an arene-rich subpocket surrounded by the aromatic side chains of Tyr179, and Trp227.

Detailed analysis of the binding mode showed that the aromatic rings point toward the aromatic rings of Tyr179 and Trp227 residues apparently developing π–π stacking interactions with the two residues. The pyrimidine backbone is located in the middle of the binding pocket, anchoring the amino substituent at C-

Table 2. Binding energies, *K*i and inhibition constant values for **4**–**13** and **16**–**27** at $T = 298.5$ K.

Ligand/Properties	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Binding energy, kcal mol^{-1}	−8.05	−8.33	−8.24	−8.19	−8.37	−8.25	−10.02	−8.92
*K*i, μM[a]	1.25	0.784	0.912	1.01	0.507	0.896	0.512	0.552
Intermolecular energy, kcal mol^{-1}	−9.62	−10.0	−9.94	−9.16	−10.50	−10.47	−10.12	−9.78
Ref. RMS[b]	21.72	23.47	22.29	22.76	20.89	23.73	22.98	23.14
Final total internal energy, kcal mol^{-1}	−0.65	−0.50	−0.50	−0.52	−0.74	−0.67	−0.61	−0.59
Torsional free energy, kcal mol^{-1}	1.79	1.79	1.79	1.78	2.09	2.39	1.87	2.11
Unbound system's energy, kcal mol^{-1}	−0.42	−0.38	−0.42	−0.39	−0.57	−0.50	−0.47	−0.50

Ligand/Properties	**12**	**13**	**16**	**17**	**18**	**19**	**20**	**21**	**22**
Binding energy, kcal mol^{-1}	−8.40	−8.49	−6.85	−7.82	−7.57	−7.88	−8.62	−6.97	−8.10
*K*i, μM[a]	0.694	0.601	9.55	1.86	2.88	2.90	2.82	2.77	3.21
Intermolecular energy, kcal mol^{-1}	−11.12	−10.75	−7.85	−8.72	−9.01	−7.92	−8.31	−7.38	−8.11
Ref. RMS[b]	23.45	24.07	33.56	30.07	30.89	31.19	30.54	31.66	30.80
Final total internal energy, kcal mol^{-1}	−0.28	−0.47	−0.65	−0.96	−1.01	−1.09	−1.78	−1.16	−2.01
Torsional free energy, kcal mol^{-1}	2.34	2.09	1.19	1.79	2.02	1.11	2.11	1.19	2.38
Unbound system's energy, kcal mol^{-1}	−0.61	−0.64	−0.47	−0.07	−0.56	−0.41	−0.68	−0.38	−0.70

Ligand/Properties	**23**	**24**	**25**	**26**	**27**
Binding energy, kcal mol^{-1}	−8.78	−8.79	−8.82	−7.61	−7.89
*K*i, μM[a]	3.19	3.17	2.81	2.64	1.64
Intermolecular energy, kcal mol^{-1}	−8.41	−8.68	−8.79	−7.97	−7.87
Ref. RMS[b]	30.18	30.59	30.81	31.64	31.05
Final total internal energy, kcal mol^{-1}	−1.91	−1.96	−2.36	−2.46	−0.28
Torsional free energy, kcal mol^{-1}	2.36	2.39	2.41	2.09	2.09
Unbound system's energy, kcal mol^{-1}	−0.72	−0.74	−0.78	−0.73	−0.69

[a] *K*i is the dissociation constant for a ligand with this binding energy; [b] reference RMS is the rms difference between this structure and the input structure.

2 in a favorable position for hydrogen bonding with the Lys101 of the reverse transcriptase (RT) enzyme. Overall, the combination of hydrophobic interaction and π–π stacking appears to govern the binding of **10** with HIV RT (binding energy -10.02 kcal mol^{-1}). Additionally, synthetic analogs in these hydrophobic domains vary mainly in the size of the C-4 alkyl group (hexyl, pentyl, Bu, Pr and Me) (**21**–**25**). These changes impact most likely the overall hydrophobicity of these inhibitors.

Experimental Section

General

Melting points are uncorrected and were measured on a Büchi melting point apparatus B-545 (Büchi Labortechnik AG, Switzerland). Microanalytical data were obtained with a Vario Elemental Analyzer (Shimadzu, Japan). NMR spectra were recorded on 400 and 600 MHz (^{1}H) and on 150.91 MHz (^{13}C) spectrometers (Bruker, Germany) with TMS as internal standard and on the δ scale in ppm. Sig-

nal assignments for protons were performed by selective proton decoupling or by COSY spectra. Heteronuclear assignments were verified by HSQC, HMBC and DFQ-COSY experiments. Mass spectra (EI, 70 eV, and FAB) were recorded on MAT 8200 spectrometers (Finnegan MAT, USA). TLC plates 60 F254 were purchased from Merck.

*General procedure for the preparation of 2-amino-6-((4-aryldiazenyl)benzyloxy)-4-chloropyrimidine derivatives **4**–**13***

A solution of substituted anilines (0.84 mmol) in 6 N HCl (4.0 mL) was cooled to 0–5 °C, and then $NaNO_2$ (58 mg, 0.84 mmol) in water (2.0 mL) was added dropwise with stirring. After the addition was completed, the solution was stirred for another 15 min and checked by iodine-starch paper. Urea (50 mg) was added to destroy the excess of HNO_2. The diazonium salt solution was then poured onto a solution of 2-amino-4-(benzyloxy)-6-chloropyrimidine (**3**) (180 mg, 0.76 mmol) in water and stirred for 30 min. Potassium acetate (485 mg) was then added, and the mixture was stirred for 16 h at room temperature. The resulting precipitate was filtered, washed with water and dried in a vacuum desiccator over P_2O_5 to give the desired azo-pyrimidine derivatives.

*2-Amino-4-chloro-6-((4-phenyldiazenyl)benzyloxy)pyrimidine (**4**)*

From aniline (78 mg). Yield: 206 mg (80 %); m. p. 160–163 °C (dec.); $R_f = 0.86$. – ^{1}H NMR ([D$_6$]DMSO): $\delta = 7.99$ (s, 2H, NH_2), 7.68–7.23 (m, 9H, $H_{arom.}$), 6.56 (s, 1H, 5-$H_{pyrimid.}$), 5.31 ppm (s, 2H, CH_2). – ^{13}C NMR ([D$_6$]DMSO): $\delta = 172.0$ ($C4_{pyrimid.}$), 162.3 ($C6_{pyrimid.}$), 161.9 ($C2_{pyrimid.}$), 151.9 ($C1''_{arom.}$), 150.7 ($C4'_{arom.}$), 137.5 ($C1'_{arom.}$), 131.9, 129.6, 127.9, 123.2 ($C_{arom.}$), 99.3 ($C5_{pyrimid.}$), 50.4 ppm (CH_2). – $C_{17}H_{14}ClN_5O$ (339.78): calcd. C 60.09, H 4.15, N 20.61; found C 60.00, H 4.06, N 20.40.

*2-Amino-6-chloro-4-(4-(p-tolyldiazenyl)benzyloxy)pyrimidine (**5**)*

From *p*-toluidine (90 mg). Yield: 223 mg (83 %); m. p. 251–254 °C (dec.); $R_f = 0.72$. – ^{1}H NMR ([D$_6$]DMSO): $\delta = 7.99$ (s, 2H, NH_2), 7.65–7.34 (m, 8H, $H_{arom.}$), 6.57 (s, 1H, 5-$H_{pyrimid.}$), 5.33 (s, 2H, CH_2), 2.28 ppm (s, 3H, CH_3). – ^{13}C NMR ([D$_6$]DMSO): $\delta = 173.4$ ($C4_{pyrimid.}$), 162.3 ($C6_{pyrimid.}$), 161.8 ($C2_{pyimid.}$), 151.8 ($C4'_{arom.}$), 148.2 ($C1''_{arom.}$), 139.3 ($C4''_{arom.}$), 137.1 ($C1'_{arom.}$), 130.1, 127.8, 123.4 ($C_{arom.}$), 99.3 ($C5_{pyrimid.}$), 50.7 (CH_2), 20.5 ppm (CH_3). – $C_{18}H_{16}ClN_5O$ (353.81): calcd. C 61.10, H 4.56, N 19.79; found C 60.87, H 4.49, N 19.57.

*4-Amino-6-chloro-4-(4-(4-chlorophenyldiazenyl)benzyloxy)pyrimidine (**6**)*

From 4-chloroaniline (107 mg). Yield: 225 mg (79 %); m. p. 236–239 °C (dec.); $R_f = 0.60$. – ^{1}H NMR ([D$_6$]DMSO): $\delta =$ 7.67–7.31 (m, 8H, $H_{arom.}$), 7.11 (s, 2H, NH_2), 6.74 (s, 1H, 5-$H_{pyrimid.}$), 5.33 ppm (s, 2H, CH_2). – ^{13}C NMR ([D$_6$]DMSO): $\delta = 173.5$ ($C4_{pyrimid.}$), 161.8 ($C6_{pyrmid.}$), 159.0 ($C2_{pyrimid.}$), 151.3 ($C4'_{arom.}$), 150.3 ($C1''_{arom.}$), 137.4 ($C1'_{arom.}$), 136.3 ($C4''_{arom.}$), 130.1, 128.6, 124.3 ($C_{arom.}$), 99.3 ($C5_{pyrimid.}$), ppm 51.1 (CH_2). – $C_{17}H_{13}Cl_2N_5O$ (374.22): calcd. C 54.56, H 3.50, N 18.71; found C 54.33, H 3.42, N 18.47.

*2-Amino-4-(4-(4-bromophenyldiazenyl)benzyloxy)-6-chloropyrimidine (**7**)*

From 4-bromoaniline (145 mg). Yield: 232 mg (73 %); m. p. 247–250 °C (dec.). $R_f = 0.75$. – ^{1}H NMR ([D$_6$]DMSO): $\delta = 7.90$ (d, 2H, $J = 8.5$ Hz, 3′-$H_{arom.}$ + 5′-$H_{arom.}$), 7.85 (d, 2H, $J = 8.4$ Hz, 3″-$H_{arom.}$ + 5″-$H_{arom.}$), 7.64 (d, 2H, $J = 8.4$ Hz, 2″-$H_{arom.}$ + 6″-$H_{arom.}$), 7.33 (d, 2H, $J = 8.5$ Hz, 2′-$H_{arom.}$ + 6′-$H_{arom.}$), 7.06 (s, 2H, NH_2), 6.56 (s, 1H, 5-$H_{pyrimid.}$), 5.37 ppm (s, 2H, CH_2). – ^{13}C NMR ([D$_6$]DMSO): $\delta = 174.3$ ($C4_{pyrimid.}$), 161.9 ($C6_{pyrimid.}$), 159.0 ($C2_{pyrimid.}$), 150.9 ($C4'_{arom.}$), 150.0 ($C1''_{arom.}$), 138.9 ($C1'_{arom.}$), 131.9, 129.6, 127.3, 125.5, 124.3, 123.2 ($C_{arom.}$), 99.3 ($C5_{pyrimid.}$), 51.1 ppm (CH_2). – $C_{17}H_{13}BrClN_5O$ (418.68): calcd. C 48.77, H 3.13, N 16.73; found C 48.56, H 3.01, N 16.70.

*2-Amino-6-chloro-4-(4-(4-nitrophenyldiazenyl)benzyloxy)pyrimidine (**8**)*

From 4-nitroaniline (116 mg). Yield: 205 mg (70 %); m. p. 270–274 °C (dec.); $R_f = 0.66$. – ^{1}H NMR ([D$_6$]DMSO): $\delta = 8.47$ (d, 1H, $J = 8.5$ Hz, 3′-$H_{arom.}$ + 5′-$H_{arom.}$), 8.09 (d, 1H, $J = 8.5$ Hz, 3″-$H_{arom.}$ + 5″-$H_{arom.}$), 7.56 (d, 1H, $J = 8.5$ Hz, 2″-$H_{arom.}$ + 6″-$H_{arom.}$), 7.35 (d, 1H, 2′-$H_{arom.}$ + 6′-$H_{arom.}$), 7.11 (s, 2H, NH_2), 6.71 (s, 1H, 5-$H_{pyrimid}$), 5.33 ppm (s, 2H, CH_2). – ^{13}C NMR ([D$_6$]DMSO): $\delta = 173.7$ ($C4_{pyrimid.}$), 162.8 ($C6_{pyrimid.}$), 160.0 ($C2_{pyrimid.}$), 154.3 ($C1''_{arom.}$), 151.3 ($C4'_{arom.}$), 150.4 ($C4''_{arom.}$), 136.2 ($C1'_{arom.}$), 128.4, 128.2, 124.1 ($C_{arom.}$), 119.6 ($C2''_{arom.}$), 101.0 ($C5_{pyrimid.}$), 51.3 ppm (CH_2). – $C_{17}H_{13}ClN_6O_3$ (384.78): C 53.07, H 3.41, N 21.84; found C 52.87, H 3.30, N 21.62.

*4-((4-((2-Amino-6-chloropyrimidin-4-yloxy)methyl)phenyl)diazenyl)phenyl methanol (**9**)*

From 4-aminobenzyl alcohol (103 mg). Yield: 191 mg (68 %); m. p. 280–284 °C (dec.); $R_f = 0.13$. – ^{1}H NMR ([D$_6$]DMSO): $\delta = 8.50–8.40$ (m, 4H, 3′-$H_{arom.}$ + 5′-$H_{arom.}$ + 3″-$H_{arom.}$ + 5″-$H_{arom.}$), 7.60–7.50 (m, 4H,

2′-$H_{arom.}$ + 6′-$H_{arom.}$ + 2″-$H_{arom.}$ + 6″-$H_{arom.}$), 6.54 (s, 1H, 5-$H_{pyrimid.}$), 5.33 (s, 2H, CH_2), 4.48 ppm (s, 2H, CH_2OD). – ^{13}C NMR ([D$_6$]DMSO-D_2O): δ = 172.8 ($C4_{pyrimid.}$), 162.6 ($C6_{pyrimid.}$), 159.2 ($C2_{pyrimid.}$), 150.3 ($C4'_{arom.}$ + $C1''_{arom.}$), 144.7 ($C4''_{arom.}$), 137.4 ($C1'_{arom.}$), 128.5, 126.5, 123.2 ($C_{arom.}$), 99.8 ($C5_{pyrimid.}$), 63.5 (CH_2OD), 51.6 ppm (CH_2). – $C_{18}H_{16}ClN_5O_2$ (369.80): calcd. C 58.46, H 4.36, N 18.94; found C 58.23, H 4.19, N 18.71.

*2-Amino-4-chloro-6-(4-(3,4-dichlorophenyldiazenyl)benzyloxy)pyrimidine (**10**)*

From 3,4-dichloroaniline (136 mg). Yield: 199 mg (70 %); m. p. 250 – 254 °C (dec.); R_f = 0.69. – ^{1}H NMR ([D$_6$]DMSO): δ = 8.37 (d, 2H, J = 7.9 Hz, 3′-$H_{arom.}$ + 5′-$H_{arom.}$), 7.90 (br s, 1H, 2″-$H_{arom.}$), 7.63 – 7.39 (m, 4H, $H_{arom.}$), 7.11 (s, 2H, NH_2), 6.64 (s, 1H, 5-$H_{pyrimid.}$), 5.51 ppm (s, 2H, CH_2). – ^{13}C NMR ([D$_6$]DMSO): δ = 173.5 ($C4_{pyrimid.}$), 162.8 ($C6_{pyrimid.}$), 160.0 ($C2_{pyrimid.}$), 151.1 ($C1''_{arom.}$), 150.3 ($C4'_{arom.}$), 138.7 ($C1'_{arom.}$), 136.2 ($C4''_{arom.}$), 130.3, 128.1, 124.8, 123.1 ($C_{arom.}$), 100.1 ($C5_{pyrimid.}$), 51.4 ppm (CH_2). – $C_{17}H_{13}Cl_2N_5O$ (374.22): calcd. C 54.56, H 3.50, N 18.71; found C 54.33, H 3.42, N 18.47.

*2-Amino-4-chloro-6-(4-((4-chloro-3-iodophenyl)diazenyl)benzyloxy)pyrimidine (**11**)*

From 4-chloro-3-iodoaniline (212 mg). Yield: 247 mg (65 %); m. p. 259 – 293 °C (dec.); R_f = 0.58. – ^{1}H NMR ([D$_6$]DMSO): δ = 8.38 d, 2H, J = 8.0 Hz, 3′-$H_{arom.}$ + 5′-$H_{arom.}$), 8.08 (br s, 1H, 2″-$H_{arom.}$), 7.91 (d, 1H, J = 8.0 Hz, 6″-$H_{arom.}$), 7.62 (d, 1H, J = 8.0 Hz, 2′-$H_{arom.}$), 7.60 (d, 1H, J = 8.0 Hz, 6′-$H_{arom.}$), 7.32 (d, 1H, J = 8.0 Hz, 5″-$H_{arom.}$), 7.05 (s, 2H, NH_2), 6.54 (s, 1H, 5-$H_{pyrimid.}$), 5.35 ppm (s, 2H, CH_2). – ^{13}C NMR ([D$_6$]DMSO): δ = 173.7 ($C4_{pyrimid.}$), 162.6 ($C6_{pyrimid.}$), 162.1 ($C2_{pyrimid.}$), 151.9 ($C1''_{arom.}$), 150.3 ($C4'_{arom.}$), 144.7 (C4″-Cl), 138.4 ($C1''_{arom.}$), 133.6 ($C2''_{arom.}$), 131.27 ($C5''_{arom.}$), 128.30 ($C2'_{arom.}$ + $C6'_{arom.}$), 122.7 ($C3'_{arom.}$ + $C5'_{arom.}$), 121.3 ($C6''_{arom.}$), 99.8 ($C5_{pyrimid.}$), 96.6 (C-I), 51.6 ppm (CH_2). – $C_{17}H_{12}ClIN_5O$ (500.12): C 40.83, H 2.42, N 14.00; found C 40.59, H 2.49, N 13.79.

*Methyl 4-((4-((2-amino-4-chloropyrimidin-4-yloxy)methyl)phenyl)diazenyl)benzoate (**12**)*

From methyl 4-aminobenzoate (127 mg). Yield: 239 mg (79 %); m. p. 136 – 140 °C; R_f = 0.15. – ^{1}H NMR ([D$_6$]DMSO): δ = 8.50 (d, 1H, J = 8.1 Hz, 3′-$H_{arom.}$ + 5′-$H_{arom.}$), 8.15 (d, 1H, J = 7.9 Hz, 2″-$H_{arom.}$ + 6″-$H_{arom.}$), 7.81 (d, 1H, J = 7.9 Hz, 3″-$H_{arom.}$ + 5″-$H_{arom.}$), 7.43 (d, 1H, J = 8.1 Hz, 2′-$H_{arom.}$ + 6′-$H_{arom.}$), 7.11 (s, 2H, NH_2), 6.71 (s, 1H, 5-$H_{pyrimid.}$), 5.33 (s, 2H, CH_2), 3.75 ppm (s, 3H, CO_2CH_3). – ^{13}C NMR ([D$_6$]DMSO): δ = 173.0 ($C4_{pyrimid.}$), 166.0 (CO_2Me); 162.6 ($C6_{pyrimid.}$), 159.2 ($C2_{pyrimid.}$), 155.5 ($C1''_{arom.}$), 150.3 ($C4'_{arom.}$), 137.5 ($C1'_{arom.}$), 131.3, 128.3, 123.2, 120.0 ($C_{arom.}$), 99.8 ($C5_{pyrimid.}$), 51.6 ppm (CH_2 + CO_2*Me*). – $C_{19}H_{16}ClN_5O_3$ (397.82): calcd. C 57.36, H 4.05, N 17.60; found C 57.09, H 3.98, N 17.38.

*N-(4-((4-((2-amino-4-chloropyrimidin-4-yloxy)methyl)phenyl)diazenyl)phenyl)acetamide (**13**)*

From 4-acetamidoaniline (126 mg). Yield: 232 mg (77 %); m. p. 110 – 114 °C; R_f = 0.10. – ^{1}H NMR ([D$_6$]DMSO): δ = 8.49 (d, 1H, J = 8.0 Hz, 3′-$H_{arom.}$ + 5′-$H_{arom.}$), 8.25 (d, 1H, J = 7.8 Hz, 2″-$H_{arom.}$ + 6″-$H_{arom.}$), 7.75 (d, 1H, J = 7.8 Hz, 3″-$H_{arom.}$ + 5″-$H_{arom.}$), 7.32 (d, 1H, J = 8.0 Hz, 2′-$H_{arom.}$ + 6′-$H_{arom.}$), 7.07 (s, 2H, NH_2), 6.69 (s, 1H, 5-$H_{pyrimid.}$), 5.36 ppm (s, 2H, CH_2). – ^{13}C NMR ([D$_6$]DMSO): δ = 173.8 ($C4_{pyrimid.}$), 167.3 (NH*CO*Me), 161.8 ($C6_{pyrimid.}$), 159.3 ($C2_{pyrimid.}$), 154.0 ($C4'_{arom.}$), 150.0 ($C1''_{arom.}$), 140.0 ($C4''_{arom.}$), 135.0 ($C1'_{arom.}$), 127.4 ($C2'_{arom.}$ + $C6'_{arom.}$), 124.3 ($C2''_{arom.}$ + $C6''_{arom.}$), 122.3 ($C3'_{arom.}$ + $C5'_{arom.}$), 115.3 ($C3''_{arom.}$ + $C5''_{arom.}$), 99.3 ($C5_{pyrimid.}$), 51.1 (CH_2), 22.9 ppm (NHCO*Me*). – $C_{19}H_{19}ClN_6O_2$ (396.83): calcd. C 57.51, H 4.32, N 21.18; found C 57.30, H 4.29, N 20.89.

*General procedure for the preparation of 2,6-diamino-5-arylazo-4-chloro-pyrimidine derivatives **15** – **20***

A solution of a substituted aniline (2.0 mmol) in 6 N HCl (6 mL) was cooled to 0 – 5 °C, and then $NaNO_2$ (138 mg, 2.0 mmol) in water (4 mL) was added dropwise with stirring. After the addition was completed, the solution was stirred for another 15 min and checked by iodine-starch paper to give a blue color. Urea (50 mg) was added to destroy the excess of HNO_2. The diazonium salt solution was then poured into a solution of 4-amino-6-chloro-1-methylpyrimidin-2-one (**14**) (260 mg, 1.80 mmol) in water (7 mL) and stirred for 30 min. Potassium acetate (700 mg, 7.14 mmol) was then added, and the mixture was stirred for 16 h at room temperature. The resulting precipitate was collected, washed with water and dried in a vacuum over P_4O_{10} to give the desired product.

*2,6-Diamino-4-chloro-5-(p-chlorophenylazo)pyrimidine (**15**)*

From 4-chloroaniline (255 mg). Yield: 407 mg (80 %); m. p. 266 – 268 °C (lit. [39]: 268 °C). All the physical data are similar to the sample prepared previously.

*2,6-Diamino-4-chloro-5-(p-bromophenylazo)pyrimidine (**16**)*

From 4-bromoaniline (344 mg). Yield: 342 mg (58 %); m. p. 227 – 230 °C; R_f = 0.65. – ^{1}H NMR ([D$_6$]DMSO): δ = 9.27 (s, 2H, NH_2), 8.16 (s, 2H, NH_2), 7.74, 7.69 ppm (2 × d, 4H, J = 8.7 Hz, H-Ar), – ^{13}C NMR ([D$_6$]DMSO):

$\delta = 165.2$ ($C2_{pyrimid.}$), 156.4 ($C6_{pyrimid.}$), 132.7 (C4-Cl), 130.6, 126.6, 123.8 ($C_{arom.}$), 119.2 ppm ($C5_{pyrimid.}$). – $C_{10}H_8BrClN_6$ (327.57): calcd. C 36.67, H 2.46, N 25.66; found C 36.89, H 2.41, N 25.47.

*2,6-Diamino-4-chloro-5-(p-nitrophenylazo)pyrimidine (**17**)*

From 4-nitroaniline (276 mg). Yield: 190 mg (36 %), m. p. 178 – 181 °C (dec.); $R_f = 0.59$. – ^{1}H NMR ([D$_6$]DMSO): $\delta = 9.40$ (s, 2H, NH_2), 8.36, 7.99 (2 × d, 4H, $J = 8.5$ Hz, H-Ar), 7.72 ppm (s, 2H, NH_2). – ^{13}C NMR ([D$_6$]DMSO): $\delta = 166.3$ ($C2_{pyrimid.}$), 156.7 ($C6_{pyrimid.}$), 147.1 (C-NO_2), 134.4 ($C_{pyrimid.}$-Cl), 132.3 ($C1_{arom.}$), 125.4, 122.6 ($C_{arom.}$), 120.1 ppm ($C5_{pyrimid.}$). – $C_{10}H_8ClN_7O_2$ (293.67): C 40.90, H 2.7, N 33.39; found C 40.71, H 2.69, N 33.18.

*Methyl 4-((2,6-diamino-4-chloropyrimidin-5-yl)diazenyl)benzoate (**18**)*

From methyl-4-aminobenzoate (302 mg). Yield: 480 mg (87 %), m. p. 160 – 164 °C; $R_f = 0.42$. – ^{1}H NMR ([D$_6$]DMSO): $\delta = 8.04$ (d, 2H, $J = 6.9$ Hz, C(6)-NH_2), 7.79, 6.89 (2 × d, 4H, $J = 8.1$ Hz, H-Ar), 6.19 (br s, 2H, C(2)-NH_2), 3.77 ppm (s, 3H, CO_2Me). – ^{13}C NMR ([D$_6$]DMSO): $\delta = 166.1$ ($C2_{pyrimid.}$), 162.3 (CO_2Me), 158.7 ($C6_{pyrimid.}$), 133.9 ($C1'_{arom.}$), 131.3 ($C4_{pyrimid.}$), 129.8, 128.9 ($C_{arom.}$), 120.1 ($C5_{pyrimid.}$), 51.6 ppm (CO_2*Me*). – $C_{12}H_{11}ClN_6O_2$ (306.71): C 46.99, H 3.61, N 27.40; found C 46.76, H 3.52, N 27.21.

*2,6-Diamino-4-chloro-5-(p-acetamidophenylazo)pyrimidine (**19**)*

From 4-acetamidoaniline (298 mg). Yield: 440 mg (76 %), m. p. 160 – 164 °C; $R_f = 0.33$. – ^{1}H NMR ([D$_6$]DMSO): $\delta = 8.85$ (br s, 1H, *NH*COMe), 8.72 (br s, 2H, C(2)-NH_2), 8.15, 6.18 (2 × d, 4H, $J = 7.8$ Hz, H-Ar), 3.75 ppm (s, 3H, NHCO*Me*). – ^{13}C NMR ([D$_6$]DMSO): $\delta = 167.5$ (NH*CO*Me), 165.6 ($C2_{pyrimid.}$), 155.0 ($C6_{arom.}$), 135.0 ($C4'_{arom.}$), 131.6 ($C_{pyrimid.}$-Cl), 130.5 ($C2'_{arom.} + C6'_{arom.}$), 126.4 ($C1'_{arom.}$), 121.4 ($C5_{pyrimid.}$), 118.6 ($C3'_{arom.} + C5'_{arom.}$), 52.5 ppm (NHCO*Me*). – $C_{12}H_{12}ClN_7O_2$ (321.72): calcd. C 44.80, H 3.76, N 30.48; found C 44.59, H 3.58, N 30.17.

*2,6-Diamino-4-chloro-5-(2-fluoro-4-nitrophenyl)azopyrimidine (**20**)*

From 2-fluoro-4-nitroaniline (345 mg). Yield: 324 mg (61 %), m. p. 262 °C; $R_f = 0.96$. – ^{1}H NMR ([D$_6$]DMSO): $\delta = 9.51$, 9.21 (2 × s, 2H, NH_2), 8.31 – 8.24 (m, 2H, H-Ar), 8.04 (m, 1H, H-Ar), 7.42 ppm (d., 2H, $J = 7.0$ Hz, NH_2). – ^{13}C NMR ([D$_6$]DMSO): $\delta = 165.3$ ($C2_{pyrimid.}$), 163.5 (d, $J_{C,F} = 247$ Hz, $C2'_{arom.}$), 156.5 ($C6_{pyrimid.}$), 141.6 (C-NO_2), 136.5 ($C_{pyrimid.}$-Cl), 128.4 ($C6'_{arom.}$), 124.4 ($C5'_{arom.}$), 122.3 (d, $J = 123$ Hz, $C1'_{arom.}$), 120.3 ($C5_{pyrimid.}$), 115.3 ppm (d, $J = 122$ Hz, $C3'_{arom.}$). – $C_{10}H_7ClFN_7O_2$ (311.66): calcd. C 38.54, H 2.26, N 31.46; found C 38.33, H 2.17, N 31.20.

*General procedure for the preparation of 2,6-diamino-4-alkylamino-5-(p-bromophenylazo)pyrimidine derivatives **21** – **27***

A solution of **16** (164 mg, 0.50 mmol) in DMF (20 mL) and an appropriate amine (1.00 mmol) was heated in an oil bath at 90 – 100 °C for 4 – 5 h. Then water (25 mL) was added, the solution was cooled, and the yellow precipitate was collected, washed with water, and dried. Recrystallization from EtOH afforded the desired product.

*2,6-Diamino-5-(p-bromophenylazo)-4-methylaminopyrimidine (**21**)*

From methylamine hydrochloride (68 mg). Yield: 124 mg (77 %), m. p. 175 – 180 °C; $R_f = 0.37$. – ^{1}H NMR ([D$_6$]DMSO): $\delta = 8.01$ (br s, 2H, NH_2), 7.72 (d, 2H $J = 7.8$ Hz, H-Ar), 7.56 (m, 3H, H-Ar + *HN*CH_3), 6.58 (br s, 2H, NH_2), 2.90 ppm (s, 3H, HN*CH_3*). – ^{13}C NMR ([D$_6$]DMSO): $\delta = 163.7$ ($C2_{pyrimid.}$), 161.6 ($C4_{pyrimid.}$), 156.8 ($C6_{pyrimid.}$), 132.2, 130.3, 127.5 ($C_{arom.}$), 123.1 (C-Br), 105.1 ($C5_{pyrimid.}$), 26.2 ppm (NMe). – $C_{11}H_{12}BrN_7$ (322.16): calcd. C 41.10, H 3.75, N 30.43; found C 40.98, H 3.57, N 30.18.

*2,6-Diamino-5-(p-bromophenylazo)-4-propylaminopyrimidine (**22**)*

From propylamine (59 mg). Yield: 154 mg (88 %), m. p. 174 – 177 °C; $R_f = 0.80$. ^{1}H NMR ([D$_6$]DMSO): $\delta = 10.42$, 8.10 (2 × br s, 2H, NH_2), 7.71 (d, 2H, $J = 7.9$ Hz, $3'$-$H_{arom.}$ + $5'$-$H_{arom.}$), 7.49 (m, 3H, $2'$-$H_{arom.}$ + $6'$-$H_{arom.}$ + CH_2*NH*), 6.38 (br s, 2H, NH_2), 3.12 (m, 2H, HN*CH_2*), 2.66 (br s, 1H, NH_{propyl}), 1.36 (m, 2H, NCH_2*CH_2*), 0.71 ppm (t, 3H, $J = 7.2$ Hz, NCH_2CH_2*CH_3*). – ^{13}C NMR ([D$_6$]DMSO): $\delta = 163.2$ ($C2_{pyrimid.}$), 162.3 ($C4_{pyrimid.}$), 152.0 ($C6_{pyrimid.}$), 131.7 ($C2' + C3' + C5' + C6'$), 122.7 ($C1'_{arom.}$), 119.0 (C-Br), 110.0 ($C5_{pyrimid.}$), 39.8 (NCH_2), 22.3 (NCH_2*CH_2*), 11.5 ppm (CH_3). – $C_{13}H_{16}BrN_7$ (350.22): calcd. C 44.58, H 4.60, N 28.00; found C 44.39, H 4.48, N 27.75.

*2,6-Diamino-5-(p-bromophenylazo)-4-butylaminopyrimidine (**23**)*

From *n*-butylamine (73 mg). Yield: 124 mg (68 %), m. p. 155 – 158 °C; $R_f = 0.88$. – ^{1}H NMR ([D$_6$]DMSO): $\delta = 10.61$, 8.50 (2 × br s, 2H, NH_2), 7.70 (d, 2H, $J = 8.0$ Hz, H-Ar), 7.55 (m, 3H, H-Ar + *HN*CH_2), 6.58 (br s, 2H, NH_2), 3.45 (m, 2H, HN*CH_2*), 1.57 (m, 2H, NCH_2*CH_2*), 1.53 (m, 2H, NCH_2CH_2*CH_2*), 0.92 ppm (t, 3H, $J = 7.0$ Hz, CH_3). – ^{13}C NMR ([D$_6$]DMSO): $\delta = 163.3$ ($C2_{pyrimid.}$), 160.8 ($C6_{pyrimid.}$), 152.0 ($C4_{pyrimid.}$), 131.7, 122.6, 118.9

($C_{arom.}$), 110.1 ($C5_{pyrimid.}$), 39.9 (NCH_2), 29.1 (NCH_2CH_2), 19.8 ($CNCH_2CH_2CH_2$), 13.5 ppm (CH_3). – $C_{14}H_{18}BrN_7$ (364.24): calcd. C 46.16, H 4.98, N 26.92; found C 45.92, H 4.80, N 26.71.

*2,6-Diamino-5-(p-bromophenylazo)-4-pentylaminopyrimidine (**24**)*

From *n*-pentylamine (87 mg). Yield: 149 mg (79 %), m. p. 158 – 162 °C; $R_f = 0.6$. – ^{1}H NMR ([D$_6$]DMSO): $\delta = 7.99$ (br s, 2H, NH_2), 7.71 (d, 2H, $J = 8.1$ Hz, H-Ar), 7.55 (m, 3H, H-Ar + $NHCH_2$), 6.57 (br s, 2H, NH_2), 3.11 (m, 2H, $HNCH_2$), 1.62 (m, 2H, NCH_2CH_2), 1.40 – 1.26 (m, 4H, $NCH_2CH_2CH_2CH_2$), 0.87 ppm (t, 3H, $J = 7.1$ Hz, CH_3). – ^{13}C NMR ([D$_6$]DMSO): $\delta = 164.0$ ($C2_{pyrimid.}$), 161.3 ($C4_{pyrimid.}$), 155.5 ($C6_{pyrimid.}$), 132.2, 131.0, 126.3 ($C_{arom.}$), 123.1 (C-Br), 110.6 ($C5_{pyrimid.}$), 43.9 (NCH_2), 31.4 (NCH_2CH_2), 29.4 ($NCH_2CH_2CH_2$), 22.6 (CH_2CH_3), 14.4 ppm (CH_3). – $C_{15}H_{20}BrN_7$ (378.27): calcd. C47.63, H 5.33, N 25.92; found C 47.41, H 5.16, N 25.71.

*2,6-Diamino-5-(p-bromophenylazo)-4-hexylaminopyrimidine (**25**)*

From *n*-hexylamine (101 mg). Yield: 165 mg (84 %), m. p. 227 – 230 °C; $R_f = 0.65$. – ^{1}H NMR ([D$_6$]DMSO): $\delta = 7.70$, 7.55 (2 × d, 4H, $J = 8.0$ Hz, H-Ar), 6.55 (br s, 2H, NH_2), 3.28 (m, 2H $HNCH_2$), 1.57 – 1.23 (m, 8H, $NCH_2(CH_2)_3$), 0.85 ppm (t, 3H, $J = 7.1$ Hz, CH_3). – ^{13}C NMR ([D$_6$]DMSO): $\delta = 163.2$ ($C2_{pyramid.}$), 161.5 ($C4_{pyrimid.}$), 156.3 ($C6_{pyrimid.}$), 132.2, 130.7 ($C_{arom.}$), 122.1 (C-Br), 105.3 ($C5_{pyrimid.}$), 42.0 (NCH_2), 29.3 (NCH_2CH_2), 29.0 ($NCH_2CH_2CH_2CH_2$), 25.6 ($NCH_2CH_2CH_2CH_2$), 22.4 (CH_2CH_3), 14.5 ppm (CH_3). – $C_{16}H_{22}BrN_7$ (392.30): calcd. C 48.99, H 5.65, N 24.99; found C 48.65, H 5.54, N 24.64.

*2,6-Diamino-5-(p-bromophenylazo)-4-hydroxyethylaminopyrimidine (**26**)*

From 2-ethanolamine (61 mg). Yield: 122 mg (69 %), m. p. 193 – 200 °C; $R_f = 0.6$. – ^{1}H NMR ([D$_6$]DMSO): $\delta = 8.01$ (br s, 2H, NH_2), 7.72, 7.56 (2 × d, 4H, $J = 7.9$ Hz, H-Ar), 6.57 (br s, 2H, NH_2), 3.53 (t, 1H, $J = 5.1$ Hz, OH), 3.41 (m, 2H, CH_2OH), 3.14 ppm (m, 2H, $HNCH_2$). – ^{13}C NMR ([D$_6$]DMSO): $\delta = 163.2$ ($C2_{pyrimid.}$), 161.1 ($C4_{pyrimid.}$), 157.7 ($C6_{pyrimid.}$), 131.7, 130.5, 128.3 ($C_{arom.}$), 122.6 (C-Br), 105.6 ($C5_{pyrimid.}$), 59.8 (CH_2OH), 47.1 ppm (NCH_2). – $C_{12}H_{14}BrN_7O$ (352.19): calcd. C 40.92, H 4.01, N 27.84; found C 40.71, H 3.90, N 27.64.

*2,6-Diamino-5-(p-bromophenylazo)-4-(2-hydroxy-1-methyl(ethyl)amino)pyrimidine (**27**)*

From 2-aminopropan-1-ol (75 mg). Yield: 117 mg (64 %), m. p. 178 – 180 °C; $R_f = 0.49$. – ^{1}H NMR ([D$_6$]DMSO): $\delta = 8.17$ (br s, 2H, NH_2), 7.75, 7.59 (2 × d, 4H, $J = 7.9$ Hz, H-Ar), 6.47 (br s, 2H, NH_2), 5.25 (br s, 1H, OH), 3.54 (m, 1H, $NCHCH_3$), 3.29 (br s, 2H, CH_2OH), 1.42 ppm (s, 3H, CH_3). – ^{13}C NMR ([D$_6$]DMSO): $\delta = 163.3$ ($C2_{pyrimid.}$), 162.0 ($C4_{pyrimid.}$), 157.2 ($C6_{pyrimid.}$), 132.4, 131.0, 128.0 ($C_{arom.}$), 123.8 (C-Br), 104.7 ($C5_{pyrimid.}$), 67.9 (CH_2OH), 58.2 ($NCHCH_3$), 17.1 ppm ($NCHCH_3$). – $C_{13}H_{16}BrN_7$ (366.22): calcd. C 42.64, H 4.40, N 26.77; found C 42.38, H 4.28, N 26.47.

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