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AMINATION OF 2-CHLORO- AND 2,4-DICHLOROPYRIMIDINES BY POLYAMINES*

A. D. Averin, O. A. Ulanovskaya, and I. P. Beletskaya

A study was carried out on the amination of 2-chloro- and 2,4-dichloropyrimidines by linear polyamines and oxadiamines under catalytic and noncatalytic conditions. The reaction of excess polyamine with 2-chloropyrimidine gives the corresponding 2-aminopyrimidines, while the reaction of polyamines with excess of 2-chloropyrimidine gives di-, tri-, and tetraarylated derivatives. The reaction of 2,4-dichloropyrimidine with diamines was studied with different ratios of the starting reagents. The ratios of the products of substitution at pyrimidine C-2 and C-4 were found.

Keywords: pyrimidines, polyamines, amination, homogeneous catalysis.

Aminopyrimidines are important heterocyclic compounds since many such derivatives are biologically active. For example, 2-(benzylamino)pyrimidine is an antihistamine. Other aminopyrimidine derivatives are commonly used as analeptics and antipellargic agents. Many aminopyrimidines are also key compounds in the synthesis of antagonists of various receptors. A variety of methods has been described for the synthesis of 2-aminopyrimidines by the nucleophilic replacement of a chlorine atom by nitrogen. Thus, Detweiler [1] and Brown [2] used a reaction with amides, while potassium carbonate has been commonly used as the base in the reaction with free amines [3, 4]. The reaction may also be carried out with excess amine without additional base [5, 6]. The reaction of 2-chloropyrimidine with allylamine was carried out with palladium catalysis [7]. Microwave radiation [8, 9] and high pressure have also been employed [10]. Tertiary amine was used as the base in the noncatalytic amination of 2-chloropyrimidine in the synthesis of antagonists of various receptors [11]. This reaction is also a key step in the synthesis of drugs for the treatment of schizophrenia [12], an antagonist for the 5-HT_{1A} receptor [13], and an NO synthase inhibitor [14].

In the amination of 2,4-dichloropyrimidines, special attention is given to selective substitution at C-2 and C-4 [15], including cases involving the use of microwave activation [16]. Both tertiary amine [16] and sodium carbonate have been used as the base [17].

Antagonist for the CRF receptor for treating depression and anxiety [18], an analog for an antagonist of the GnRH receptor for treating prostatis and breast cancer [19], and many other drugs with high pharmaceutical activity have been developed starting from aminochloropyrimidines.

* Dedicated to Academician B. A. Trofimov on the occasion of his seventieth jubilee.

M. V. Lomonosov Moscow State University, Moscow 119992, Russia, e-mail: averin@org.chem.msu.ru.
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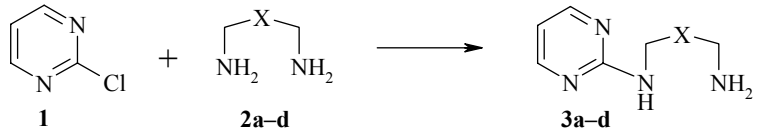
In a systematic study of the arylation of polyamines by aryl halides carried out in our laboratory in recent years [20-24] and in an attempt to expand the range of arylating agents, we have investigated the amination of 2-chloropyrimidine (**1**) using di-, tri-, and tetraamines **2a-e**. Literature data indicate that the amination of 2-chloropyrimidine by monoamines can be achieved without catalysis and, thus, we initially studied the reaction of this substrate with polyamines under noncatalytic conditions. The reaction of 2-chloropyrimidine **1** with three equivalents of polyamines **2a-d** was used for the synthesis of mono(pyrimidinyl)polyamines **3**.

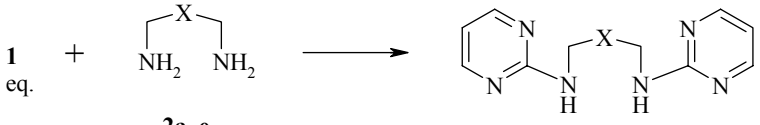


1 **2a–d** 3 eq. **3a–d**

2, 3 **a** X = CH_2, **b** X = $(CH_2)_2NH(CH_2)_2$, **c** X = $CH_2O(CH_2)_2OCH_2$,
d X = $(CH_2)_2O(CH_2)_2O(CH_2)_2O(CH_2)_2$

The reactions were carried out in dioxane at reflux using triethylamine taken in large excess (10 equivalents) as the base and were complete after 5 h. The yields of the desired products **3** depend strongly on the structure of the amine. The greatest yield was achieved for **3b** (Table 1, No. 2), while much lower yields were obtained for dioxa- and trioxadiamines. This result is related to the significant formation of side bis(pyrimidinyl)polyamines **4** despite the considerable excess of polyamine in the reaction mixture.

A twofold excess of 2-chloropyrimidine relative to polyamines **2** was taken in the planned synthesis of bis(pyrimidinyl)polyamines **4**. Cesium carbonate was used throughout as the base since, in this case, it proved better than triethylamine (in contrast to the previous reaction, in which triethylamine provides for better results than Cs_2CO_3). Furthermore, in some cases, the reaction was carried out under standard catalytic conditions using 4 mol% $Pd(dba)_2$–4.5 mol% BINAP (BINAP = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) [25]. However, in comparing the results for the reactions with triamine **2b**, we found that the use of catalyst did not significantly increase the yield of **4b** although the time required for complete conversion of the polyamine was cut approximately in half.



2a–e **4a–e**

2, 4 **e** X = $(CH_2)_2NH(CH_2)_2NH(CH_2)_2$

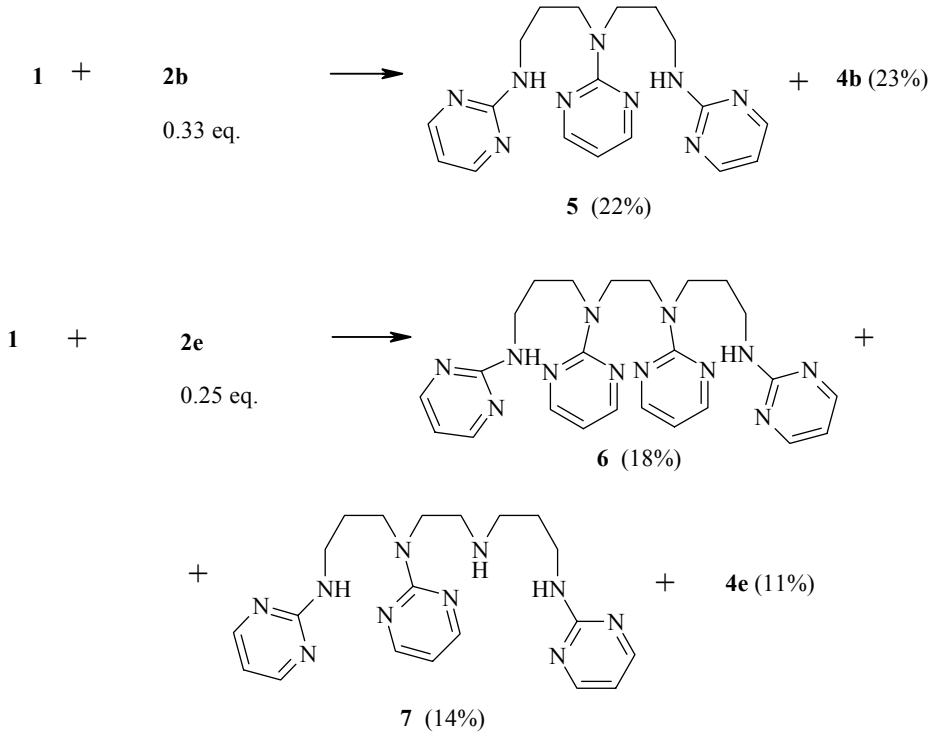
The data on the reaction conditions and product yields are given in Table 1. The greatest yields are found for the reactions using diamines (Nos. 5, 8, and 9). The yields of the corresponding diarylated products for the reactions with triamine **2b** and tetraamine **2d** are lower since side tri- and tetraarylated polyamines **5-7** (Nos. 7 and 10) are formed. We should note that, in contrast to the reactions with previously studied haloarenes, arylation of the internal nitrogen atoms in the polyamines occurs rather than diarylation of the terminal nitrogen atoms. Furthermore, an attempt to synthesize tetra- or tripyrimidinyldiaminopropane using a large excess of 2-chloropyrimidine was unsuccessful.

TABLE. 1. Synthesis of N-(2-Pyrimidinyl)polyamines **3** and N^{α},N^{ω}-Bis-(2-pyrimidinyl)polyamines **4**

No	Starting reagents		**1** : **2**	$Pd(dba)_2$/ BINAP, mol. %	Base	Yield, %*	Side-products, %
	halopyrimidine	amine					
1	**1**	**2a**	1 : 3	—	Et_3N	**3a** (49)	**4a** (24)
2	**1**	**2b**	1 : 3	—	Et_3N	**3b** (76)	
3	**1**	**2c**	1 : 3	—	Et_3N	**3c** (18)	**4c** (28)
4	**1**	**2d**	1 : 3	—	Et_3N	**3d** (35)	**4d** (24)
5	**1**	**2a**	2 : 1	4/4.5	Cs_2CO_3	**4a** (50)	
6	**1**	**2b**	2 : 1	4/4.5	Cs_2CO_3	**4b** (24)	**5** (27)
7	**1**	**2b**	2 : 1	—	Cs_2CO_3	**4b** (19)	**5** (20)
8	**1**	**2c**	2 : 1	—	Cs_2CO_3	**4c** (53)	
9	**1**	**2d**	2 : 1	4/4.5	Cs_2CO_3	**4d** (71)	
10	**1**	**2e**	2 : 1	4/4.5	Cs_2CO_3	**4e** (29)	**6** (4), **7** (8)

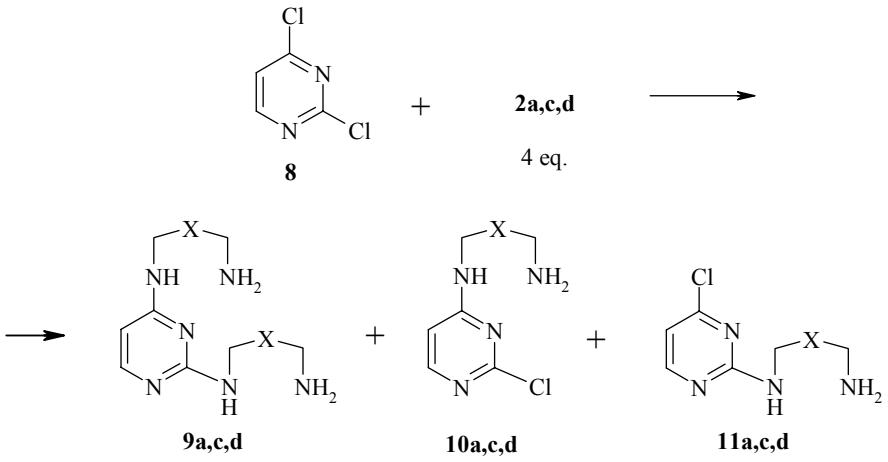
* The yields after chromatography are given in parentheses.

The reaction of triamine **2b** with three equivalents of 2-chloropyrimidine led to the formation of both tri- and diarylated products and the yield of the desired product **5** was even somewhat lower than in the synthesis of diarylated triamine **4b**. The reaction of tetraamine **2e** with four equivalents of 2-chloropyrimidine also led to the formation of a mixture of tetra-, tri-, and dipyrimidinyl derivatives **6, 7,** and **4e**, respectively.



Various workers [15-17] have shown that in most aminations of 2,4-dichloropyrimidine **8** by monoamines, the reaction preferentially proceeds at C-4 of the pyrimidine although in some cases, different regioorientation or competition between two substitution pathways was observed. Hence, we initially studied

the feasibility of synthesizing 2,4-bis(polyamino)pyrimidines using diamines **2a, 2c**, and **2d** as the amines in order to achieve a less complicated reaction pathway (there are no secondary amino groups in these compounds) as well as for the convenience of separating the less polar reaction products using column chromatography.



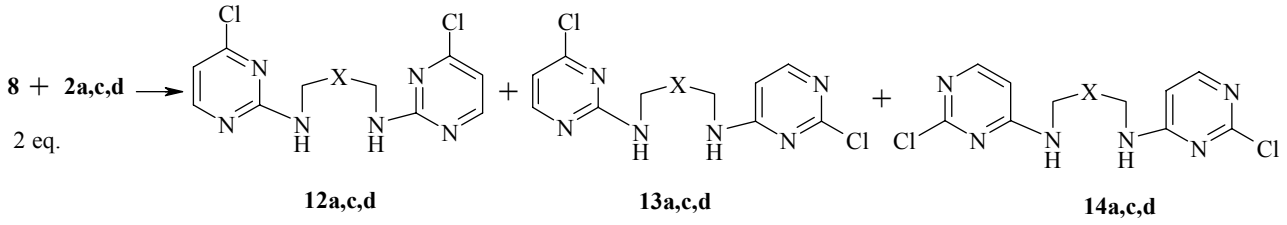
The corresponding bis(polyamino) derivatives **9** are formed when four equivalents of diamine are used. These products are obtained in moderate yields and isomeric monoamination products **10** and **11**, which are 4-amino-2-chloropyrimidines and 2-amino-4-chloropyrimidines, respectively, are obtained as side products. In this reaction, the 4-amino derivatives **10** are formed more readily than 2-amino derivatives **11** (Table 2, Nos. 1 and 2). The reasons for assigning the structures of isomers **10** and **11** using ^{1}H NMR spectroscopy are analogous to the those given below for bis(chloropyrimidinyl)polyamines.

TABLE 2. Synthesis of 2,4-Bis(polyamino)pyrimidines **9** and Bis(chloropyrimidinyl)diamines **12** and **14**

No	Starting reagents		**8** : **2**	Base	Yield, %*	Side products, %
	halopyrimidine	amine				
1	**8**	**2a**	1:4	Et_3N	**9a** (35)*[2]	**10a** (50)*[2], **11a** (15)*[2]
2	**8**	**2c**	1:4	Et_3N	**9c** (48)	**10c** (27), **11c** (9)
3	**8**	**2d**	1:4	Et_3N	**9d** (50)	**11d** (22)
4	**8**	**2a**	2:1	Cs_2CO_3	**12a** (15), **13a** (22), **14a** (29)	
5	**8**	**2a**	2:1*[3]	Cs_2CO_3	**12a** (19), **13a** (37), **14a** (9)	
6	**8**	**2a**	2:1	Et_3N	**12a** (31), **13a** (15), **14a** (54)	
7	**8**	**2c**	2:1	Cs_2CO_3	**12c** (11), **13c** (14), **14c** (3)	
8	**8**	**2d**	2:1	Cs_2CO_3	**12d** (7), **13d** (28), **14d** (21)	

* The yields after chromatography are given in parentheses.
*[2] The percentage of the compounds in the fraction soluble in $CDCl_3$.
**[3] The $Pd(dba)_2$/BINAP (4/4.5 mol%) catalytic system was used.

The reaction of two equivalents of 2,4-dichloropyrimidine **8** with the same diamines leads to the formation of a mixture of the three possible diarylated products **12-14**.



Some differences in the isomer depending on the structure of the diamine are noted when using cesium carbonate as the base in the absence of catalyst. While, the ratio of diaminopropane **2a** to trioxadiamine **2d** clearly indicates a preference for replacement of the chlorine atom at C-4 in the pyrimidine (Table 2, Nos. 4 and 8), the opposite behavior is observed for dioxadiamine **2c** (Table 2, No. 7). The use of catalyst, which did not play a significant role in the reactions with 2-chloropyrimidine, leads in this case to a change in the isomer ratio (No. 5): the percentage of replacement of the chlorine atom at pyrimidine C-2 is enhanced. The structural assignments of **12, 13**, and **14** were based on the ^{1}H and ^{13}C NMR spectral data. The signals for the pyrimidine protons H-5 at 6.48-6.54 ppm and for H-6 at 8.07-8.13 ppm are characteristic for the 2-amino-4-chloro-pyrimidines. The signals for the methylene group protons in the diamine fragments substituted by a 4-chloropyrimidinyl group are not broadened. The ^{13}C NMR spectra also show narrow signals for the pyrimidine and aliphatic carbon atoms. On the other hand, the signals for pyrimidine protons H-5 at 6.22-6.31 ppm and H-6 at 7.91-7.96 ppm are characteristic for 4-amino-2-chloropyrimidines. The signals of the methylene group protons in the diamine fragments substituted by 4-chloropyrimidinyl groups are markedly broadened and appear as broad singlets. The ^{13}C NMR spectra also show broadened signals for the tertiary pyrimidinyl carbon atoms and aliphatic carbon atoms located next to the 2-chloropyrimidinyl substituent. These data permit us to distinguish between the 2-amino-4-chloropyrimidine and 4-amino-2-chloropyrimidine substituents as well as the directly attached diamine fragments. However, pyrimidine protons H-5 in these compounds are also sensitive to the type of substitution in the other pyrimidine ring at the opposite nitrogen atom of the diamine, which permits an unequivocal assignment for all three isomers. Thus, for example, this proton in the 2-amino-4-chloropyrimidine ring in compound **12c** is found at 6.51 ppm and it appears at 6.54 ppm in compound **13c**. On the other hand, this proton in the 4-amino-2-chloropyrimidine ring is found at 6.22 ppm in compound **13c** and at 6.21 ppm in compound **14c**.

Thus, the amination of 2-chloro- and 2,4-dichloropyrimidines by linear polyamines is feasible both without catalyst and in the presence of a palladium catalyst. The reaction rate is enhanced by the catalyst and the ratio of the products of substitution at C-2 and C-4 may be altered in the case of 2,4-dichloropyrimidine. The predominant formation of products of mono- and polyarylation of the polyamines as well as of the products of mono- and diamination of 2,4-dichloropyrimidine may be achieved by altering the ratio of the starting reagents.

EXPERIMENTAL

All the operations related to the synthesis of nitrogen-containing pyrimidine derivatives were carried out in a dry argon atmosphere using purified solvents. Absolute dioxane and triethylamine were prepared by heating at reflux and distillation over KOH with subsequent distillation over sodium. Dichloromethane was distilled over calcium hydride. Methanol was distilled. Commercial samples of the starting reagents were used without further purification. Polyamines, cesium carbonate, BINAP, 2-chloropyrimidine, and 2,4-dichloro-

pyrimidine were obtained from Aldrich and Acros. A sample of $Pd(dba)_2$ was prepared from palladium chloride according to a method described by Ibers et al. [26]. Fluka 40-60 μm silica gel was used for the chromatography. The ^1H and ^{13}C NMR spectra were taken on Varian VXR-400 and Bruker Avance-400 spectrometers at 400 and 100 MHz, respectively, in $CDCl_3$ (for products **3-7, 9c, 9d,** and **11-14**). The MALDI-TOF spectra were obtained on a Bruker Daltonics Autoflex II instrument.

N-(2-Pyrimidinyl)polyamines 3 (General Method). A mixture of 2-chloropyrimidine **1** (0.5 mmol), 3 eq. corresponding polyamine **2**, absolute dioxane (5 ml), and triethylamine (505 mg, 5 mmol, 0.7 ml) was heated at reflux in an argon stream for 5 h, cooled to room temperature, evaporated in vacuum, and subjected to chromatography on a silica gel column using the following sequence of eluents: CH_2Cl_2, 100:1-3:1 CH_2Cl_2–MeOH, and 100:20:1 – 10:3:1 CH_2Cl_2–MeOH–NH_3.

N-(2-Pyrimidinyl)propane-1,3-diamine (3a). The reaction of compound **1** (57 mg, 0.5 mmol) and propanediamine **2a** (111 mg, 1.5 mmol) gave 37 mg (49%) compound **3a** as a colorless oil, CH_2Cl_2–MeOH–NH_3, 10:3:1, was used as the eluent. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.74 (2H, q, $^3J = 6.7$, CCH_2C); 2.65 (2H, br. s, NH_2); 2.81 (2H, t, $^3J = 6.6$, $C\underline{H}_2NH_2$); 3.47 (2H, q, $^3J = 6.2$, $C\underline{H}_2NHAr$); 5.76 (1H, br. s, NHAr); 6.45 (1H, t, $^3J = 4.8$, H-5); 8.21 (2H, d, $^3J = 4.8$, H-4, H-6). ^{13}C NMR spectrum, δ, ppm: 32.39 (1C); 39.04 (1C); 39.40 (1C); 110.29 (1C); 157.95 (2C); 162.48 (1C). MALDI-TOF mass spectrum (ditranol), *m/z*: 153.05 $[M+H]^+$. $C_7H_{13}N_4$. Calculated: 153.11.

The reaction also gave 14 mg (24%) bis(pyrimidinyl)propanediamine **4a** as a side product. This compound was eluted with 10:1 CH_2Cl_2–MeOH.

N-[3-(2-Pyrimidinylamino)propyl]propane-1,3-diamine (3b). The reaction of 2-chloropyrimidine (57 mg, 0.5 mmol) and triamine **2b** (197 mg, 1.5 mmol) gave 73 mg (76%) compound **3b** as a colorless oil. The eluent CH_2Cl_2–MeOH–NH_3, 10:3:1, was used. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.65 (2H, q, $^3J = 6.7$, CCH_2C); 1.75 (2H, q, $^3J = 6.4$, CCH_2C); 2.66 (2H, t, $^3J = 6.5$, $C\underline{H}_2NHCH_2$); 2.69 (2H, t, $^3J = 6.4$, $C\underline{H}_2NHCH_2$); 2.78 (2H, t, $^3J = 6.7$, $C\underline{H}_2NH_2$); 3.42 (2H, q, $^3J = 5.0$, $C\underline{H}_2NHAr$); 3.64 (3H, br. s, NH_2, CNHC); 5.98 (1H, br. s, NHAr); 6.42 (1H, t, $^3J = 4.6$, H-5); 8.18 (2H, d, $^3J = 4.6$, H-4, H-6). ^{13}C NMR spectrum, δ, ppm: 29.09 (1C); 31.95 (1C); 39.68 (1H, 40.04 (1C); 47.40 (1C); 47.55 (1C); 110.13 (1C); 157.89 (2C); 162.38 (1C). MALDI-TOF mass spectrum (ditranol), *m/z*: 210.05 $[M+H]^+$. $C_{10}H_{20}N_5$. Calculated: 210.17.

N-{2-[2-(2-Aminoethoxy)ethoxy]ethyl}pyrimidine-2-amine (3c). The reaction of 2-chloropyrimidine (57 mg, 0.5 mmol) and dioxadiamine **2c** (222 mg, 1.5 mmol) gave 20 mg (18%) compound **3c** as a colorless oil. The eluent CH_2Cl_2–MeOH–NH_3, 100:20:3, was used. ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.51 (2H, br. s, NH_2); 2.87 (2H, t, $^3J = 4.4$, $C\underline{H}_2NH_2$); 3.50 (2H, t, $^3J = 5.2$, $C\underline{H}_2NHAr$); 3.56-3.66 (8H, m, CH_2O); 5.79 (1H, br. s, NHAr); 6.47 (1H, t, $^3J = 4.8$, H-5); 8.22 (2H, d, $^3J = 4.8$, H-4, H-6). ^{13}C NMR spectrum, δ, ppm: 41.10 (1C); 41.46 (1C); 69.83 (1C); 70.23 (1C); 70.30 (1C); 72.82 (1C); 110.45 (1C); 157.95 (2C); 162.30 (1C). MALDI-TOF Mass spectrum (ditranol), *m/z*: 226.95 $[M+H]^+$. $C_{10}H_{19}N_4O_2$. Calculated: 227.15.

The reaction also gave bis(pyrimidinyl)dioxadiamine **4c** 21 mg (28%). This product was eluted with 10:1 CH_2Cl_2–MeOH.

N-(3-{2-[2-(3-Aminopropoxy)ethoxy]ethoxy}propyl)pyrimidine-2-amine (3d). The reaction of 2-chloropyrimidine (57 mg, 0.5 mmol) and trioxadiamine **2d** (330 mg, 1.5 mmol) gave 52 mg (35%) compound **3d** as a colorless oil. The eluent CH_2Cl_2–MeOH–NH_3, 10:20:3, was used. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.65 (2H, q, $^3J = 6.4$, CCH_2C); 1.81 (2H, q, $^3J = 6.3$, CCH_2C); 2.47 (2H, br. s, NH_2); 2.72 (2H, t, $^3J = 6.7$, $C\underline{H}_2NH_2$); 3.42 (2H, q, $^3J = 6.4$, $C\underline{H}_2NHAr$); 3.47 (2H, t, $^3J = 6.2$, $NCCCH_2O$); 3.48-3.59 (10H, m, CH_2O); 5.79 (1H, br. s, NHAr); 6.40 (1H, t, $^3J = 4.7$, H-5); 8.16 (2H, d, $^3J = 4.7$, H-4, H-6). ^{13}C NMR spectrum, δ, ppm: 29.09 (1C); 32.67 (1C); 38.90 (1C); 39.29 (1C); 69.25 (2C); 69.98 (1C); 70.08 (1C); 70.39 (2C); 109.99 (1C); 157.78 (2C); 162.24 (1C). MALDI-TOF mass spectrum, *m/z*: 299.04 $[M+H]^+$. $C_{14}H_{27}N_4O_3$. Calculated: 299.21.

The reaction also gave 23 mg (24%) bis(pyrimidinyl)trioxadiamine **4d**. This product was eluted with CH_2Cl_2–MeOH, 10:1.

N^{α},N^{ω}-Bis(2-pyrimidinyl)polyamines (General Method). A mixture of compound **1** (1 mmol), corresponding polyamine **2** (0.5 mmol), absolute dioxane (5 ml), and cesium carbonate (340 mg, 1 mmol) was heated at reflux in an argon stream for 5 h, cooled to room temperature, evaporated in vacuum, and subjected to chromatography on a silica gel column using the following sequence of eluents: CH_2Cl_2; CH_2Cl_2–MeOH, 100:1 – 3:1; CH_2Cl_2–MeOH–NH_3, 100:20:1 – 10:3:1.

N,N'-Di(2-pyrimidinyl)propane-1,3-diamine (4a). The reaction of compound **1** (115 mg, 1 mmol) and propanediamine **2a** (36 mg, 0.5 mmol) in the presence of $Pd(dba)_2$ (4 mol%, 24 mg), BINAP (4.5 mol%, 28 mg), and cesium carbonate (1 mmol, 340 mg,) gave 58 mg (50%) compound **4a** as light-beige crystals.. The reaction mixture was subjected to chromatography on a silica gel column using the following sequence of eluents: CH_2Cl_2; CH_2Cl_2–MeOH, 500:1 – 3:1. The product was eluted with CH_2Cl_2–MeOH, 25:1; mp 101-103°C ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.84 (2H, q, ^3J = 6.4, CCH_2C); 3.49 (4H, q, ^3J = 6.3, $C\underline{H}_2NH$); 6.02 (2H, br. s, NH); 6.44 (2H, t, ^3J = 4.8, H-5); 8.22 (4H, d, ^3J = 4.8, H-4, H-6). ^{13}C NMR spectrum, δ, ppm: 29.69 (1C); 38.33 (2C); 110.19 (2C); 157.92 (4C); 162.46 (2C). MALDI-TOF mass spectrum (ditranol), *m/z* 230.99 $[M+H]^+$. $C_{11}H_{15}N_6$. Calculated: 231.14.

N-(2-Pyridiminyl)-N'-[3-(2-pyrimidinylamino)propyl]propane-1,3-diamine (4b). A. The reaction of compound **1** (115 mg, 1 mmol) and triamine **2b** (65.5 mg, 0.5 mmol) in the presence of $Pd(dba)_2$ (4 mol%, 24 mg), BINAP (4.5 mol%, 28 mg), and cesium carbonate (340 mg, 1 mmol) gave 35 mg (24%) compound **4b**. Product was eluted with CH_2Cl_2–MeOH–NH_3, 100:20:3.

This reaction also gave 49 mg (27%) tris(pyrimidinyl)triamine **5**, which was eluted with CH_2Cl_2–MeOH, 3:1.

B. The reaction of compound **1** (115 mg, 1 mmol) and triamine **2b** (65.5 mg, 0.5 mmol) in the presence of cesium carbonate (340 mg, 1 mmol) gave 27 mg (19%) compound **4b** as light-beige crystals. This product was eluted with CH_2Cl_2–MeOH–NH_3, 100:20:3; mp 145-147°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.81 (4H, q, ^3J = 6.4, CCH_2C); 2.73 (4H, t, ^3J = 6.4, $C\underline{H}_2NHCH_2$); 3.46 (4H, q, ^3J = 5.3, $C\underline{H}_2NHAr$); 6.17 (2H, br. s, NHAr); 6.44 (2H, t, ^3J = 4.8, H-5); 8.21 (4H, d, ^3J = 4.8, H-4, H-6). ^{13}C NMR spectrum, δ, ppm: 28.87 (2C); 39.59 (2C); 47.19 (2C); 110.18 (2C); 157.93 (4C); 162.43 (2C). MALDI-TOF mass spectrum (ditranol), *m/z*: 288.03 $[M+H]^+$. $C_{14}H_{22}N_7$. Calculated: 288.19.

This reaction also gave 37 mg (20%) compound **5**, which was eluted with CH_2Cl_2–MeOH, 10:1.

N-(2-{2-[2-(2-Pyrimidinylamino)ethoxy]ethoxy}ethyl)-2-pyrimidineamine (4c). The reaction of compound **1** (229 mg, 2 mmol) and dioxadiamine **2c** (148 mg, 1 mmol) in the presence of cesium carbonate (680 mg, 2 mmol) gave 160 mg (53%) compound **4c** as light-beige crystals. This product was eluted with CH_2Cl_2–MeOH, 10:1; mp 87-89°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.50-3.57 (8H, m, $NCCH_2O$, $C\underline{H}_2NH$); 3.52 (4H, s, OCH_2CO); 6.34 (2H, br. s, NH); 6.37 (2H, t, ^3J = 4.8, H-5); 8.15 (4H, d, ^3J = 4.8, H-4, H-6). ^{13}C NMR spectrum, δ, ppm: 40.94 (2C); 69.89 (2C); 70.24 (2C); 110.03 (2C); 157.76 (4C); 162.25 (2C). MALDI-TOF Mass spectrum (ditranol), *m/z*: 305.00 $[M+H]^+$. $C_{14}H_{21}N_6O_2$. Calculated: 305.17.

N-[3-(2-{2-[3-(2-Pyrimidinylamino)propoxy]ethoxy}ethoxy)propyl]-2-pyrimidineamine (4d). The reaction of 2-chloropyrimidine (115 mg, 1 mmol) and trioxatriamine **2d** (108 mg, 0.5 mmol) in the presence of $Pd(dba)_2$ (4 mol%, 24 mg), BINAP (4.5 mol%, 28 mg), and cesium carbonate (340 mg, 1 mmol) gave 133 mg (71%) compound **4d** as light-beige crystals. This product was eluted with CH_2Cl_2–MeOH, 10:1 and 3:1; mp 63-65°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.82 (4H, q, ^3J = 6.3, CCH_2C); 3.43 (4H, q, ^3J = 6.3, $C\underline{H}_2NH$); 3.52 (4H, t, ^3J = 6.1, $NCCCH_2O$); 3.52-3.55 (4H, m, CH_2O); 3.57-3.60 (4H, m, CH_2O); 5.86 (2H, br. s, NH); 6.40 (2H, t, ^3J = 4.8, H-5); 8.17 (4H, d, ^3J = 4.8, H-4, H-6). ^{13}C NMR spectrum, δ, ppm: 28.99 (2C); 38.69 (2C); 69.01 (2C); 69.94 (2C); 70.27 (2C); 109.76 (2C); 157.58 (4C); 162.19 (2C). MALDI-TOF mass spectrum (ditranol), *m/z*: 377.04 $[M+H]^+$. $C_{14}H_{21}N_6O_2$. Calculated: 377.23.

N^1-(2-Pyrimidinyl)-N^3-(2-{[3-(2-pyrimidinylamino)propyl]amino}ethyl)-1,3-propanediamine (4e). The reaction of 2-chloropyrimidine (115 mg, 1 mmol) and tetraamine **2e** (87 mg, 0.5 mmol) in the presence of $Pd(dba)_2$ (4 mol%, 24 mg), BINAP (4.5 mol%, 28 mg), and cesium carbonate (340 mg, 1 mmol) gave 48 mg (29%) compound **4e** as a colorless oil. This product was eluted with CH_2Cl_2–MeOH–NH_3, 10:3:1. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.81 (4H, q, ^3J = 6.5, CCH_2C); 2.81 (4H, t, ^3J = 6.5, $NCCC\underline{H_2}NH$); 2.87 (4H, s, $NHC\underline{H_2}CN$); 3.49 (4H, q, ^3J = 6.0, $C\underline{H_2}NHAr$); 4.20 (2H, br. s, $CH_2N\underline{H}CH_2$); 5.86 (2H, br. s, NHAr); 6.48 (2H, t, ^3J = 4.8, H-5); 8.24 (4H, d, ^3J = 4.8, H-4, H-6). ^{13}C NMR spectrum, δ, ppm: 28.70 (2C); 39.34 (2C); 46.88 (2C); 47.87 (2C); 110.45 (2C); 158.04 (4C); 162.48 (2C). MALDI-TOF mass spectrum (ditranol), *m/z*: 331.07 $[M+H]^+$. $C_{16}H_{27}N_8$. Calculated: 331.24.

This reaction also gave side products, tris(pyrimidinyl)tetraamine **6** (4% yield obtained upon elution with CH_2Cl_2–MeOH–NH_3, 100:20:1) and tetrakis(pyrimidinyl)tetraamine **7** (8% yield obtained upon elution with CH_2Cl_2–MeOH, 3:1).

N,N'-Di(2-pyrimidinyl)-N-[3-(2-pyrimidinylamino)propyl]propane-1,3-diamine (5). A mixture of 2-chloropyrimidine (172 mg, 1.5 mmol), triamine **2b** (65.5 mg, 0.5 mmol), $Pd(dba)_2$ (4 mol%, 35 mg) BINAP (4.5 mol%, 41 mg), absolute dioxane (5 ml), and cesium carbonate (500 mg, 1.5 mmol) was refluxed in an argon stream for 5 h, cooled to room temperature and evaporated in vacuum. The residue was subjected to chromatography on a silica gel column using the following sequence of eluents: CH_2Cl_2; CH_2Cl_2–MeOH, 100:1 – 3:1; CH_2Cl_2–MeOH–NH_3, 100:20:1 – 100:20:2. The product was eluted with CH_2Cl_2–MeOH, 10:1. This reaction gave 41 mg (22%) compound **5** as a colorless oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.86 (4H, q, ^3J = 6.5, CCH_2C); 3.39 (4H, q, ^3J = 6.2, CH_2NHAr); 3.67 (4H, t, ^3J = 6.7, $CH_2N(Ar)C$); 6.12 (2H, br. s, NHAr); 6.42 (1H, t, ^3J = 4.8, H-5'); 6.44 (2H, t, ^3J = 4.5, H-5); 8.21 (4H, d, ^3J = 4.5, H-4, H-6). ^{13}C NMR spectrum, δ, ppm: 27.57 (2C); 38.32 (2C); 44.43 (2C); 109.29 (1C); 110.08 (2C); 157.65 (2C); 157.92 (4C); 161.79 (1C); 162.41 (2C). MALDI-TOF mass spectrum (ditranol), *m/z*: 366.01. $C_{18}H_{24}N_9$. Calculated: 366.22.

This reaction also gave 33 mg (23%) bis(pyrimidinyl)triamine **4b** as a side product, which was eluted with CH_2Cl_2–MeOH–NH_3, 100:20:2.

N^1,N^3-Di(2-pyrimidinyl)-N^1-(2-{2-pyrimidinyl[3-(2-pyrimidinylamino)propyl]amino}ethyl)-1,3-propanediamine (7). A mixture of 2-chloropyrimidine (228 mg, 2 mmol), tetraamine **2e** (87 mg, 0.5 mmol), absolute dioxane (5 ml), and triethylamine (2.8 mg, 20 mmol) was heated at reflux in an argon stream for 5 h, cooled to room temperature, evaporated in vacuum, and subjected to chromatography using the following sequence of eluents: CH_2Cl_2; CH_2Cl_2–MeOH, 100:1 – 3:1; CH_2Cl_2–MeOH–NH_3, 100:20:1-10:3:1. The product was eluted with CH_2Cl_2–MeOH, 10:1. The reaction gave 44 mg (18%) compound **7** as light-yellow crystals, mp 150-152°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.89 (4H, q, ^3J = 6.4, CCH_2C); 3.39 (4H, q, ^3J = 6.1, $C\underline{H_2}NHAr$); 3.72 (4H, t, ^3J = 6.6, $CH_2N(Ar)C$); 3.76 (4H, s, NCH_2CN); 6.18 (2H, br. s, NHAr); 6.43 (2H, t, ^3J = 4.7, H-5'); 6.44 (2H, t, ^3J = 4.7, H-5); 8.22 (4H, d, ^3J = 4.7, H-4, H-6); 8.29 (4H, d, ^3J = 4.7, H-4', H-6'). ^{13}C NMR spectrum, δ, ppm: 27.73 (2C); 38.23 (2C); 45.31 (4C); 109.38 (2C); 110.05 (2C); 157.69 (4C); 157.93 (4C); 161.72 (2C); 162.48 (2C). MALDI-TOF mass spectrum, *m/z*: 487.03 $[M+H]^+$. $C_{24}H_{31}N_{12}$. Calculated: 487.28.

N,N'-Di(2-pyrimidinyl)-N-(2-{[3-(2-pyrimidinylamino)propyl]amino}ethyl)propane-1,3-diamine (6) was obtained as a side product. The yield of compound **6** was 48 mg (14%) as a yellow oil, which was eluted with CH_2Cl_2–MeOH–NH_3, 100:20:3 . ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.82 (2H, q, ^3J = 6.4, CCH_2C); 1.88 (2H, q, ^3J = 6.3, CCH_2C); 2.78 (2H, t, ^3J = 6.4, CH_2N); 2.90 (2H, t, ^3J = 6.4, CH_2N); 3.35-3.49 (4H, m, CH_2N); 3.72 (4H, t, ^3J = 6.2, CH_2N); 5.80 (1H, br. s, NHAr); 6.14 (1H, br. s, NHAr); 6.41-6.46 (3H, m, H-5, H-5', H-5''); 8.21 (2H, d, ^3J = 4.9, H-4, H-6); 8.22 (2H, d, ^3J = 5.2, H-4', H-6'); 8.27 (2H, d, ^3J = H-4'', H-6''); 1NH proton could not be assigned unequivocally. ^{13}C NMR spectrum, δ, ppm: 27.24 (1C); 29.20 (1C); 38.32 (1C); 39.53 (1C); 45.37 (1C); 47.13 (1C); 47.21 (1C); 47.48 (1C); 109.57 (1C); 110.13 (1C); 110.34 (1C), 157.65 (2C); 157.97 (4C); 161.83 (1C); 162.48 (2C). MALDI-TOF mass spectrum, *m/z*: 409.04. $C_{20}H_{29}N_{10}$. Calculated: 409.26.

This reaction gave an additional 18 mg (11%) side product, bis(pyrimidinyl)tetraamine **4e**, which was eluted with CH_2Cl_2–MeOH–NH_3, 10:3:1.

Synthesis of 2,4-Bis(polyamino)pyrimidines 9 (General Method). A. A mixture of 2,4-dichloropyrimidine **8** (0.5 mmol), corresponding polyamine **2** (2 mmol), absolute dioxane (5 ml), and triethylamine (10 mmol) was heated at reflux in an argon stream for 5 h, cooled to room temperature, evaporated in vacuum, and subjected to chromatography on a silica gel column using the following sequence of eluents: CH_2Cl_2; CH_2Cl_2–MeOH, 50:1 – 3:1; CH_2Cl_2–MeOH–NH_3; 100:20:1 – 10:3:1.

N,N'-Bis(3-aminopropyl)pyrimidine-2,4-diamine (9a) was obtained from 2,4-dichloropyrimidine (75 mg, 0.5 mmol) and propanediamine **2a** (144 mg, 2 mmol) in the presence of triethylamine (1.4 ml, 10 mmol). The reaction mixture was partially soluble in $CDCl_3$, partially soluble in DMSO-d_6. The content of compound **9a** in these fractions was 35 and 40 mol %, respectively. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.58 (4H, q, ^3J = 6.6, CCH_2C); 2.86 (4H, t, ^3J = 6.1, $C\underline{H}_2NH_2$); 3.42 (4H, q, ^3J = 6.2, $C\underline{H}_2NHAr$); 5.64 (1H, d, ^3J = 5.5, H-5); 7.77 (1H, d, ^3J = 5.5, H-6); 6NH protons could not be unequivocally assigned. ^{1}H NMR spectrum (DMSO-d_6); δ, ppm (*J*, Hz): 1.62 (4H, q, ^3J = 5.5, CCH_2C); 2.63 (4H, t, ^3J = 6.6, $C\underline{H}_2NH_2$); 3.24 (4H, br. s, $C\underline{H}_2NHAr$); 5.67 (1H, d, ^3J = 5.5, H-5); 7.59 (1H, br. s, H-6); 6NH protons could not be assigned unequivocally. ^{13}C NMR spectrum (DMSO-d_6); δ, ppm: 30.88 (1C); 31.03 (1C); 37.78 (1C); 38.10 (1C); 38.30 (1C); 38.39 (1C); 104.94 (1C); 154.93 (1C); 162.08 (1C); 162.61 (1C).

A mixture of isomers **10a** (50 mol %) and **11a** (15 mol %) was also found in the fraction in $CDCl_3$.

N,N'-Bis{2-[2-(2-aminoethoxy)ethoxy]ethyl}pyrimidine-2,4-diamine (9c). The reaction with 2,4-dichloropyrimidine (75 mg, 0.5 mmol) and dioxadiamine **2c** (296 mg, 2 mmol) in the presence of triethylamine (1.4 ml, 10 mmol) gave 89 mg (48%) compound **9c** as a colorless oil. The product was eluted with CH_2Cl_2–MeOH–NH_3, 10:3:1. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.55 (4H, br. s, NH_2); 2.76 (4H, br. s, $C\underline{H}_2NH_2$); 3.46-3.55 (20H, m, CH_2O, $C\underline{H}_2NHAr$); 5.40 (2H, br. s, NHAr); 5.61 (1H, d, ^3J = 5.8, H-5); 7.64 (1H, d, ^3J = 5.8, H-6). ^{13}C NMR spectrum, δ, ppm: 39.90 (1C); 40.43 (1C); 40.61 (1C); 40.90 (1C); 68.79 (1C); 69.03 (1C); 69.17 (1C); 69.53 (1C); 69.60 (2C); 72.45 (1C); 72.53 (1C); 109.09 (1C); 158.53 (1C); 161.63 (1C); 162.48 (1C). MALDI-TOF mass spectrum (ditranol), *m/z*: 373.06 $[M+H]^+$. $C_{16}H_{33}N_6O_4$. Calculated: 373.26.

This reaction also gave compounds **10c** (yield 27 %) and **11c** (yield 9% using CH_2Cl_2–MeOH–NH_3, 10:3:1, as eluent.

N,N'-Bis(3-{2-[2-(3-aminopropoxy)ethoxy]ethoxy}propyl)pyrimidine-2,4-diamine (9d). The reaction of 2,4-dichloropyrimidine (75 mg, 0.5 mmol), trioxadiamine **2d** (440 mg, 2 mmol), and triethylamine (1.4 ml, 10 mmol) gave 128 mg (50%) compound **9d** as a colorless oil. This product was eluted with CH_2Cl_2–MeOH–NH_3, 10:3:1. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.58 (4H, q, ^3J = 6.4, CCH_2C); 1.69 (4H, br. s, CCH_2C); 2.64 (4H, t, ^3J = 6.4, $C\underline{H}_2NH_2$); 2.69 (4H, br. s, NH_2); 3.36-3.50 (28H, m, $C\underline{H}_2NHAr$, CH_2O); 4.87 (1H, s, NHAr); 5.22 (1H, s, NHAr); 5.53 (1H,d, ^3J = 5.8, H-5); 7.57 (1H, d, ^3J = 5.8, H-6). ^{13}C NMR spectrum, δ, ppm: 28.77 (1C); 29.28 (1C); 32.40 (1C); 32.45 (1C); 38.37 (1C); 38.97 (1C); 39.02 (2C); 69.01 (4C); 69.75 (2C); 69.82 (2C); 70.14 (4C); 94.16 (1C); 155.05 (1C); 161.81 (1C); 162.78 (1C). MALDI-TOF mass spectrum (ditranol), *m/z*: 517.11 $[M+H]^+$. $C_{24}H_{49}N_6O_6$. Calculated: 517.37.

N-{2-[2-(2-Aminoethoxy)ethoxy]ethyl}-4-chloro-2-pyrimidineamine (11d) was obtained in 22% yield (37 mg) as a colorless oil as a side-product eluted with CH_2Cl_2–MeOH–NH_3, 100:20:3. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.88 (2H, q, ^3J = 6.0, CCH_2C); 2.01 (2H, q, ^3J = 5.0, CCH_2C); 3.19 (2H, t, ^3J = 5.0, $C\underline{H}_2NH_2$); 3.59 (12H, br. s, $C\underline{H}_2NHAr$, CH_2O); 3.66 (2H, t, ^3J = 5.0, CH_2O); 6.47 (1H, d, ^3J = 5.2, H-5); 8.10 (1H, d, ^3J = 5.2, H-6); 3NH protons could not be assigned unequivocally. ^{13}C NMR spectrum, δ, ppm: 26.42 (1C); 28.44 (1C); 38.14 (1C); 39.69 (1C); 69.06 (1C); 69.68 (1C); 69.73 (1C); 69.86 (1C); 69.97 (1C); 70.28 (1C); 109.45 (1C); 154.94 (1C); 159.00 (1C); 163.80 (1C). MALDI-TOF mass spectrum (ditranol), 332.99 $[M+H]^+$. $C_{14}H_{26}ClN_4O_3$. Calculated: 333.17.

Reaction of 2,4-Dichloropyrimidine with Diamines (General Method). A mixture of 2,4-dichloropyrimidine **8** (149 mg, 1 mmol), corresponding diamine (0.5 mmol) in absolute dioxane (5 ml), and the calculated amount of base (cesium carbonate or triethylamine) was heated at reflux for 5 h in an argon

stream and cooled. The solvent was evaporated off in vacuum and the residue was subjected to chromatography on a silica gel column using the following sequence of eluents: CH_2Cl_2; CH_2Cl_2–MeOH, 100:1 – 3:1; CH_2Cl_2–MeOH–NH_3, 100:20:1 – 100:20:2.

Reaction of 2,4-dichloropyrimidine with propanediamine 2a. A. The reaction of 2,4-dichloropyrimidine (149 mg, 1 mmol) and propanediamine **2a** (36 mg, 0.5 mmol) in the presence of cesium carbonate (340 mg, 1 mmol) gave a 1:1.5:1.5 mixture of isomers (67 mg), namely, N^1,N^3-bis(4-chloro-2-pyrimidinyl)-1,3-propanediamine (**12a**), N^1-(2-chloro-4-pyrimidinyl)-N^3-(4-chloro-2-pyrimidinyl)-1,3-propanediamine (**13a**), and N^1,N^3-bis(2-chloro-4-pyrimidinyl)-1,3-propanediamine (**14a**) upon elution with CH_2Cl_2–MeOH, 25:1. The reaction also gave pure isomer **14a** (6.5 mg) as a colorless oil upon elution with CH_2Cl_2–MeOH, 10:1. The total yield of **14a** was 29%. The yield of compound **12a** was 15% and the yield of compound **13a** was 22%.

Propanediamine 14a. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.86 (2H, q, ^3J = 6.3, CC<u>H</u>$_2$C); 3.51(4H, q, ^3J = 6.3, C<u>H</u>$_2$NHAr); 5.95 (2H, br. s, NHAr); 6.31 (2H, d, ^3J = 5.5, H-5); 7.96 (2H, d, ^3J = 5.5, H-6). ^{13}C NMR spectrum, δ, ppm: 29.25 (1C, br. s); 37.20 (2C, br. s); 110.38 (2C, br. s); 156.20 (2C, br. s); 160.81 (2C); 163.75 (2C). MALDI-TOF mass spectrum (ditranol), *m/z*: 298.15 $[M+H]^+$. $C_{11}H_{12}Cl_2N_6$. Calculated: 298.05.

B. The reaction of 2,4-dichloropyrimidine (149 mg, 1 mmol) and propanediamine (36 mg, 0.5 mmol) in the presence of $Pd(dba)_2$ (4 mol%, 24 mg), BINAP (4.5 mol%, 28 mg), and cesium carbonate (340 mg, 1 mmol) gave 11 mg (19%) compound **12a** as a colorless oil. This product was eluted with CH_2Cl_2–MeOH, 25:1. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.85 (2H, q, ^3J = 6.4, CCH_2C); 3.51 (4H, q, ^3J = 6.3 C<u>H</u>$_2$NHAr); 5.80 (2H, br. s, NHAr); 6.52 (2H, d, ^3J = 4.9, H-5); 8.12 (2H, d, ^3J = 4.9, H-6). ^{13}C NMR spectrum, δ, ppm: 29.62 (1C); 38.48 (2C); 109.92 (2C); 159.07 (2C); 162.54 (2C); 163.56 (2C). MALDI-TOF mass spectrum (ditranol), *m/z*: 298.05 $[M+H]^+$. $C_{11}H_{12}Cl_2N_6$. Calculated: 298.05.

This reaction also gave 54 mg of a 0.25:1 mixture of isomers **13a** (37% yield) and **14a** (9% yield) eluted with 10:1 CH_2Cl_2–MeOH.

Propanediamine 13a. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.86 (2H, q, ^3J = 5.6, CCH_2C); 3.45 (2H, br. s, CH_2NHAr); 3.52 (2H, q, ^3J = 6.3, C<u>H</u>$_2$NHAr); 5.95 (1H, br. s, NHAr); 6.24 (1H, d, ^3J = 5.4, H-5); 6.30 (1H, br. s, NHAr); 6.54 (1H, d, ^3J = 5.2, H-5'); 7.91 (1H, br. s, H-6); 8.12 (1H, d, ^3J = 4.9, H-6'). ^{13}C NMR spectrum, δ, ppm: 29.22 (1C); 38.38 (2C); 105.31 (1C, br. s); 110.09 (1C); 156.23 (1C, br. s); 159.20 (1C); 161.34 (1C); 162.64 (1C); 163.68 (1C); 163.79 (1C).

B. The reaction of 2,4-dichloropyrimidine (149 mg, 1 mmol) and propanediamine (36 mg, 0.5 mmol) in the presence of triethylamine (1.4 ml, 20 mmol) gave a 2:1:3.5 mixture of compound **12a** (31% yield), compound **13a** (15% yield), and compound **14a (**54% yield).

Reaction of 2,4-Dichloropyrimidine with Dioxadiamine 2c. The reaction of 2,4-dichloropyrimidine (149 mg, 1 mmol) and dioxadiamine **2c** (74 mg, 0.5 mmol) in the presence of cesium carbonate (680 mg, 2 mmol) gave a 1:1 mixture of isomers **12c** and **13c** (32 mg). This mixture was eluted with CH_2Cl_2–MeOH, 25:1. The reaction also gave 10 mg of a 1:0.9 mixture of compound **13c** and compound **14c** eluted with CH_2Cl_2–MeOH, 10:1. The total yield of **12c** was 16 mg (11%). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.57-3.68 (12H, m, CH_2O, CH_2N); 6.51 (2H, d, ^3J = 5.2, H-5); 8.13 (2H, d, ^3J = 5.2, H-6); 2NH protons could not be assigned unequivocally. ^{13}C NMR spectrum, δ, ppm: 41.25 (2C); 69.89 (2C); 70.51 (2C); 109.78 (2C); 159.09 (2C); 161.30 (2C); 162.39 (2C).

The total yield of compound **13c** was 21 mg (14%). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 3.57-3.68 (12H, m, CH_2O, CH_2N); 6.22 (1H, d, ^3J = 5.6, H-5); 6.54 (1H, d, ^3J = 5.1, H-5'); 7.91 (1H, br. s, H-6); 8.12 (1H, br. s, H-6'); 2NH protons could not be assigned unequivocally. ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 40.88 (1C, br. s); 41.10 (1C); 69.46 (2C); 70.16 (1C); 70.51 (1C); 104.32 (1C, br. s); 109.98 (1C); 156.22 (1C, br. s); 159.09 (1C); 161.30 (1C); 162.27 (1C); 162.39 (1C); 163.63 (1C).

The total yield of compound **14c** was 5 mg (3%). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 3.57-3.68 (12H, m, CH_2O, CH_2N); 6.21 (2H, d, ^3J = 5.3, H-5); 7.91 (2H, br. s, H-6); 2NH protons could not be

assigned unequivocally. ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 40.83 (2C, br. s); 69.07 (2C, br. s); 70.14 (2C); 104.20 (2C, br. s); 156.14 (2C, br. s); 160.57 (2C); 163.58 (2C). MALDI-TOF mass spectrum (ditranol), *m/z*: 372.90 $[M+H]^+$. $C_{14}H_{18}Cl_2N_6O_2$. Calculated: 373.09.

Reaction of 2,4-Dichloropyrimidine with Trioxadiamine 2d. The reaction of 2,4-dichloropyrimidine (149 mg, 1 mmol) and trioxadiamine **2d** (110 mg, 0.5 mmol) in the presence of cesium carbonate (680 mg, 2 mmol) gave of a 1:3 mixture of isomers **12d** and **13d** (49 mg). This mixture was eluted with CH_2Cl_2–MeOH, 25:1. This reaction also gave 56 mg of a 1:2.5 mixture of isomers **13d** and **14d** eluted with CH_2Cl_2–MeOH, 10:1. The yield of compound **12d** was 12 mg (7%). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.84 (4H, q, ^3J = 5.8, CCH_2C); 3.48 (4H, q, ^3J = 5.6, $C\underline{H}_2NHAr$); 3.56 (4H, t, ^3J = 5.7, $NCCCH_2O$); 3.57-3.62 (4H, m, CH_2O); 3.62-3.67 (4H, m, CH_2O); 5.85 (2H, br. s, NHAr); 6.48 (2H, d, ^3J = 4.6, H-5); 8.07 (2H, d, ^3J = 4.6, H-6). ^{13}C NMR spectrum, δ, ppm: 28.98 (2C); 39.48 (2C); 69.48 (2C); 70.30 (2C); 70.50 (2C); 109.53 (2C); 158.96 (2C); 161.13 (2C); 162.37 (2C).

The reaction also gave 53 mg (28%) compound **13d**. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.84 (4H, q, ^3J = 5.8, CCH_2C); 3.48 (4H, q, ^3J = 5.6, $C\underline{H}_2NHAr$); 3.56 (4H, t, ^3J = 5.7, $NCCCH_2O$); 3.57-3.62 (4H, m, CH_2O); 3.62-3.67 (4H, m, CH_2O); 5.85 (1H, br. s, NHAr); 6.13 (1H, br. s, NHAr); 6.21 (1H, d, ^3J = 5.4, H-5); 6.47 (1H, d, ^3J = 4.6, H-5'); 7.92 (1H, br. s, H-6); 8.07 (1H, d, ^3J = 4.6, H-6'). ^{13}C NMR spectrum, δ, ppm: 28.43 (1C, br. s); 28.98 (1C); 39.48 (1C); 39.82 (1C); 69.52 (1C); 70.13 (1C); 70.26 (1C); 70.50 (2C); 70.60 (1C); 104.24 (1C, br. s); 109.62 (1C); 155.68 (1C, br. s); 158.96 (1C); 160.76 (1C); 161.13 (1C); 162.37 (1C); 163.67 (1C).

This reaction also gave 40 mg (21%) compound **14d**. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.82 (4H, q, ^3J = 5.7, CCH_2C); 3.42 (4H, br. s, $C\underline{H}_2NHAr$); 3.51-3.60 (8H, m, CH_2O); 3.60-3.65 (4H, m, CH_2O); 6.20 (2H, br. s, NHAr); 6.22 (2H, d, ^3J = 5.5, H-5); 7.91 (2H, br. s, H-6). ^{13}C NMR spectrum, δ, ppm: 28.50 (2C); 39.61 (2C); 70.08 (2C); 70.40 (4C); 104.38 (2C, br. s); 155.52 (2C, br. s); 160.64 (2C); 163.67 (2C). MALD-TOF Mass spectrum (ditranol), *m/z*: 444.92 $[M+H]^+$. $C_{18}H_{27}Cl_2N_6O_3$. Calculated: 445.15.

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