PYRIMIDINE DERIVATIVES STARTING FROM DICYANOKETENE ETHYLENE ACETAL

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Abstract - Dicyanoketene ethylene acetal (**1**) reacted with substituted guanidines to yield *o*-aminocyanopyrimidines, which reacted with *N,N*-dimethylformamide dimethyl acetal to afford *N,N*-dimethylamino-methyleneaminopyrimidine derivatives. A new approach to pyrimido[4,5-*d*]pyrimidines from *o*-aminocyanopyrimidine and *N*-dichloromethylenedialkyliminum chorides followed by cyclization with ammonium hydroxide was reported.

INTRODUCTION

In 1988, we reported a convenient method for the preparation of by that time unknown 2-alkyloxycarbonylcyanomethylene-1,3-dioxolane.[1] From then on, we have succeeded to synthesize a series of heterocyclic compounds starting from 2-alkyloxycarbonyl-cyanomethylene- and dicyanomethylene-1,3-dioxolanes, such as substituted pyrazoles,[2,4,5] isoxazoles,[2,5] pyrimidones[2,3] and pyrimidines.[5]

Because of their high reactivity, amide acetals are used for organic synthesis. Using amide acetals Stanovnik *et al.* prepared a variety of heterocycles.[6]

Phosgeneiminium chlorides are valuble strong electrophilic one carbon reagents. Recently from *N,N*-dichloromethylenedialkyliminium chlorides and dicyano compounds, we have synthesized a series of new heterocycles.[7]

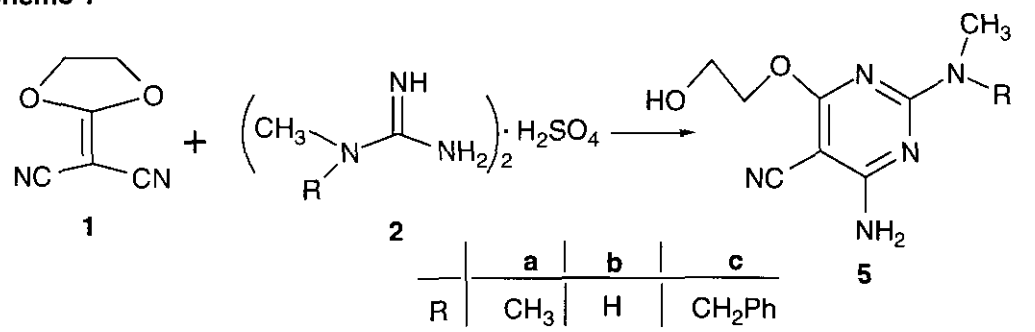
This paper describes our attempts to synthesize several pyrimidine and pyrimido[4,5-*d*]pyrimidine derivatives using dicyanoketene ethylene acetal (**1**), *N*-substituted guanidine salts (**2**), *N,N*-dimethylformamide dimethyl acetal (**3**) and *N*-dichloromethylenedialkyliminium chlorides (**4**).

RESULTS AND DISCUSSION

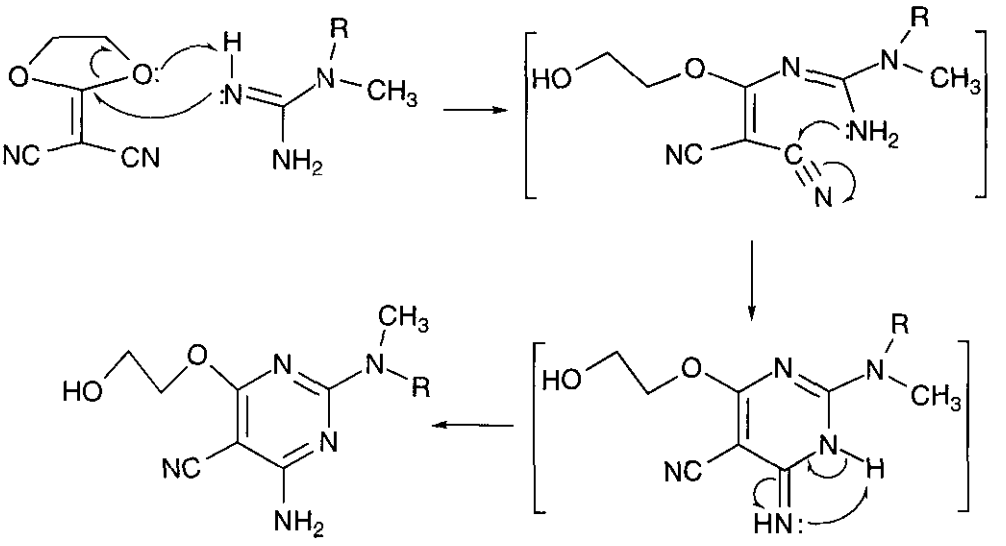
As an extention of our preparation of pyrimidine derivatives, we treated dicyano ketene ethylene acetal (**1**) with *N*-substituted guanidine salts (**2a-c**), which are easily available by

the method of Phillips and Clarke,[8] to yield pyrimidines (**5a-c**) (Scheme 1). Their IR, MS, ^{1}H- and ^{13}C-NMR spectra as well as elemental analyses data are consistent with their structures. The mechanism of these reactions may probably be described as shown in Scheme 2.

Scheme 1

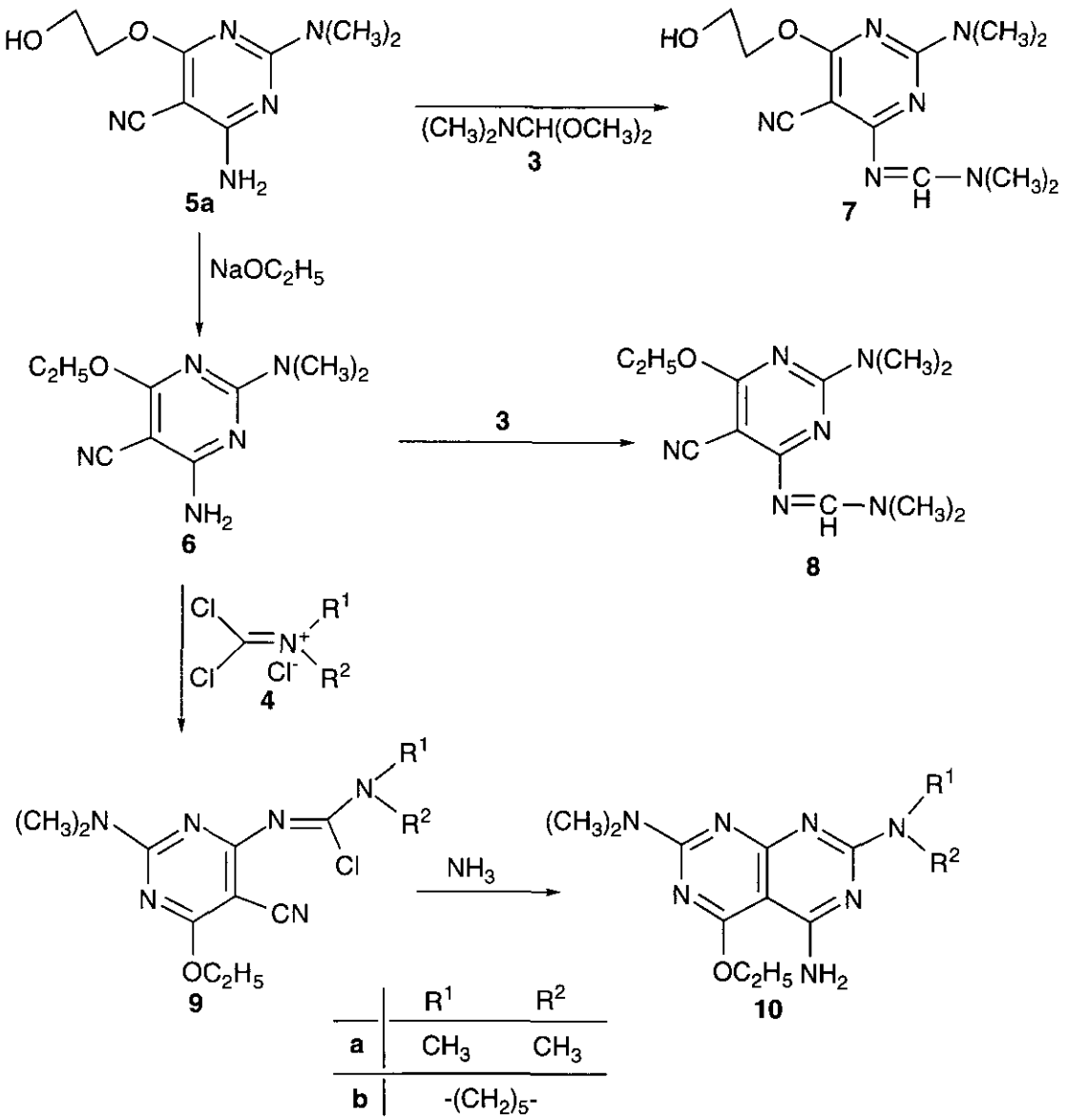


Scheme 2



Treatment of **5a** with sodium ethoxide in ethanol under reflux afforded 4-amino-5-cyano-2-dimethylamino-6-ethoxypyrimidine (**6**) in good yield. The ^{1}H-NMR spectrum of **6** shows that the signals of CH_2OH [3.71 ppm (q, J= 5.4 Hz, 2H, C**H**$_2$OH); 4.85 ppm (t, J= 5.1 Hz, 1H, CH_2O**H**)] disappeared, and it has a new CH_3 signal [at 1.30 ppm (t, J= 6.9 Hz, 3H, OCH_2C**H**$_3$)]. **5a** and **6** reacted with *N,N*-dimethylformamide dimethyl acetal (**3**) in toluene under reflux to yield 4-(dimetylaminomethyleneamino)pyrimidines (**7**) and (**8**), respectively (see Scheme 3). In their ^{1}H-NMR spectra, the signals of NH_2 group at 6.99 and 7.01 ppm vanished, in the meanwhile a signal of azomethino proton at 8.61 ppm emerged. Unfortunately, **7** and **8** did not react with α-bromo ketone such as phenacyl bromide as well

Scheme 3



as hydrazine and hydroxylamine to the expected bicyclic heterocycles, even though Stanovnik *et al.* reported preparations of a series of bicyclic heterocyclic compounds from *reactants containing N,N-dimethylaminomethyleneamino substitutent under similar* conditions.[6]

Since the synthesis of pyrimido[4,5-*d*]pyrimidine was described in 1958,[10] only few papers have been reported about this bicyclic system. Now we present another approach to this system.

It is known, that α-amino nitriles react with phosgeneiminium chloride under reflux giving

(dimethylamino-chloro)azomethino group-containing intermediates, which undergo cyclization to the formation of pyrimidine derivatives *via* reaction with dry hydrogen chloride.[11] But the treatment of **6** with *N*-dichloromethylenedialkyliminium chlorides (**4**) afforded only **9**, although enough hydrogen chloride gas was passed under reflux, no cyclized products were observed. The absorption of CN (2214 cm^{-1}) in IR spectra, and signals of C-atom in (chloro-dimethylamino)azomethino group (about 140 ppm) in ^{13}C-NMR spectra confirm the structures. Otherwise we had the similar observation in our early work.[7c] **9** reacted consequently with ammonium hydroxide to yield substituted 4-aminopyrimido[4,5-*d*]pyrimidines (**10**) (see Scheme 3). In their ^{1}H-NMR spectra the NH_2 signals appeared and in ^{13}C-NMR spectra the signals of C-atom at about 140 ppm and CN at 116 ppm in azomethino group vanished.

EXPERIMENTAL

Melting points were determined on a Reichert hot microscope and are uncorrected. IR spectra were measured with a Perkin-Elmer spectrophotometer 283 using potassium bromide and are given as cm^{-1}. ^{1}H- and ^{13}C-NMR spectra were recorded on either a Bruker WM-250 (^{1}H-NMR: 250.13 MHz, ^{13}C-NMR: 62.89 MHz), Bruker WM-360 (^{1}H-NMR: 360 MHz, ^{13}C-NMR: 90.56 MHz) or a Varian XL 300 (^{1}H-NMR: 299.95 MHz, ^{13}C-NMR: 75.43 MHz) spectrometer in DMSO-d_6 or $CDCl_3$. The chemical shifts are reported in parts per million (ppm) downfield from internal tetramethylsilane. Electron impact MS spetra were obtained on a Varian MAT 311A instrument. Element analyses were performed on a Heraeus Vario EL CHNS apparatus.

General procedure for preparation of 5a-c:

To a stirred solution of sodium methoxide in methanol, prepared by dissolving sodium (0.115 g, 5 mmol) in methanol (20 mL), **2** (2.5 mmol) was added. After 5 min, **1** (0.68 g, 5 mmol) was added to the reaction mixture. The mixture was refluxed for 5 h, then cooled to -20°C overnight, the precipitates were collected by filtration and recrystallized from water/methanol to give the corresponding products.

4-Amino-5-cyano-2-dimethylamino-6-(2-hydroxyethoxy)pyrimidine (5a) 78%. mp 185-188°C. IR (KBr): 3404, 3336, 3245 (NH, OH); 2212 (CN); 1656, 1601, 1569, 1544 (C=C, C=N); 1140, 1069 (C-O). ^{1}H-NHR (300 MHz, DMSO-d_6): δ= 3.08 (s, 6H, N(**C**H_3)$_2$); 3.71 (q, J= 5.4 Hz, 2H, HO**C**H_2CH$_2$); 4.34 (t, J= 5.4 Hz, 2H, **C**H_2CH$_2$OH); 4.85 (t, J= 5.1 Hz, 1H, **OH**); 6.99 (s, 2H, N**H**$_2$). ^{13}C-NMR (75.43 MHz, DMSO-d_6): δ= 38.9 (-, N(**C**H_3)$_2$); 59.1 (+, **C**H_2OH); 62.1 (+, C-5); 67.7 (+, O**C**H_2CH$_2$OH); 116.0 (+, **C**N); 160.6 (+, C-2); 165.1 (+, C-4); 170.0 (+, C-6). MS m/z (%): $[M+1]^+$: 224 (7.4); M^+: 223 (56.7); 180 (40); 179 (70); 164 (48); 150 (41); 71 (29); 44 (100). HRMS: Calcd for $C_9H_{13}N_5O_2$: 223.1069. Found: 223.1069. *Anal.* Calcd for $C_9H_{13}N_5O_2$: C, 48.42; H, 5.87; N, 31.37. Found: C, 48.28; H, 5.90; N, 30.91.

4-Amino-5-cyano-6-(2-hydroxyethoxy)-2-methylaminopyrimidine (5b) 62.2%. mp 215-217°C. IR (KBr): 3387, 3133 (NH, OH); 2204 (CN); 1669, 1615, 1564 (C=N, C=C); 1464, 1433; 1335; 1191; 1108, 1075 (C-O). ^{1}H-NMR (300 MHz, DMSO-d_6): δ= 3.18 (s, 3H, NC**H**$_3$); 3.65 (t, J= 5.1 Hz, 2H, C**H**$_2$); 4.27 (t, J= 5.4 Hz, 2H, C**H**$_2$); 4.85 (br s, 1H, N**H**CH$_3$); 7.94 (br s, 2H, N**H**$_2$). ^{13}C-NMR (75.43 MHz, DMSO-d_6): δ= 29.6 (-, N**C**H$_3$); 59.2 (+, **C**H$_2$); 64.7 (+, C-5), 67.9 (+, **C**H$_2$); 117.0 (+, **C**N); 156.4 (+, C-4); 157.2 (+, C-2); 168.2 (+, C-6). MS m/z (%): [M+1]$^+$: 210 (9.6); M$^+$: 209 (88); 166 (44); 165 (100); 124 (86); 123 (50); 57 (86); 43 (43). HRMS: Calcd for $C_8H_{11}N_5O_2$: 209.0912. Found: 209.0911. *Anal.* Calcd for $C_8H_{11}N_5O_2$: C, 45.93; H, 5.30; N, 33.48. Found: C, 46.14; H, 5.39; N, 33.01.

4-Amino-2-benzylmethylamino-5-cyano-6-(2-hydroxyethoxy)pyrimidine (5c) 57.5%. mp 167-170°C. IR (KBr): 3377, 3336 (NH); 3230(OH); 2216(CN); 1659, 1595, 1540 (C=C, C=N); 1494, 1471, 1450, 1423, 1403; 1139, 1070 (C-O); 921, 784, 726, 695 (arom.). ^{1}H-NMR (300 MHz, DMSO-d_6): δ= 3.05 (s, 3H, NC**H**$_3$); 3.67 (q, J= 4.8 Hz, 2H, C**H**$_2$OH); 4.33 (m, 2H, C**H**$_2$O); 4.82 (d, J= 6.6 Hz, 2H, NC**H**$_2$Ph); 4.86 (d, J= 6.3 Hz, 1H, O**H**); 7.12 (s, 2H, N**H**$_2$); 7.24-7.36 (m, 5H, Harom.). ^{13}C-NMR (75.43 MHz, DMSO-d_6): δ= 34.4 (-, N**C**H$_3$); 51.3 (+, N**C**H$_2$Ph); 58.9 (+, **C**H$_2$OH); 62.5 (+, C-5), 67.7 (+, **C**H$_2$O); 115.7 (+, **C**N); 126.8, 127.1, 128.2 (-, C-2′,3′,4′); 137.7 (+, C-1′); 160.6 (+, C-2); 165.1 (+, C-4); 170.1 (+, C-6). MS m/z (%): [M+1]$^+$: 300 (12); M$^+$: 299 (68); 255 (20); 240 (65); 164 (49); 120 (47); 106 (24); 91 (100); 65 (26); 42 (15). *Anal.* Calcd for $C_{15}H_{17}N_5O_2$: C, 60.19; H, 5.73; N, 23.40. Found: C, 60.08; H, 5.71; N, 23.34.

4-Amino-5-cyano-2-dimethylamino-6-ethoxypyrimidine (6):

To a stirred solution of sodium ethoxide, prepared by dissolving sodium (46 mg, 2 mmol) in ethanol (20 mL), **5a** (0.45 g, 2 mmol) was added. After heating and refluxing for 18 h, the solvent was removed under reduced pressure. The residue was washed with water to give 0.41 g (99%) of **6**. mp >300°C. IR (KBr): 3406, 3346, 3237 (NH); 2210 (CN); 1653, 1602, 1563, 1528 (C=N, C=C); 1345, 1288, 1257 (C-N); 1139 (C-O). ^{1}H-NMR (300 MHz, DMSO-d_6): δ= 1.30 (t, J= 6.9 Hz, 3H, CH$_2$C**H**$_3$); 3.09 (s, 6H, N(C**H**$_3$)$_2$); 4.36 (q, J= 6.9 Hz, 2H, C**H**$_2$CH$_3$); 7.01 (s, 2H, N**H**$_2$). ^{13}C-NMR (75.43 MHz, DMSO-d_6): δ= 14.27 (-, CH$_2$**C**H$_3$); 36.19 (-, N**C**H$_3$); 36.20 (-, N**C**H$_3$); 59.0 (+, C-5); 61.8 (+, **C**H$_2$CH$_3$); 115.9 (+,**C**N); 160.5 (+, C-2); 164.9 (+, C-4); 169.7 (+, C-6). MS m/z (%): [M+1]$^+$: 208 (12); M$^+$: 207 (99.7); 192 (43); 179 (42); 164 (63); 150 (54); 135 (27); 71 (29); 44 (100). HRMS: Calcd for $C_9H_{13}N_5O$: 207.1121. Found: 207.1122. *Anal.* Calcd for $C_9H_{13}N_5O$: C, 52.16; H, 6.32; N, 33.79. Found: C, 51.93; H, 6.28; N, 33.56.

General procedure for preparation of 7 and 8:

A solution of **5a** or **6** (5 mmol) and *N,N*-dimethylformamide dimethyl acetal (**3**) (0.60 g, 5

mmol) in toluene (10 mL) was refluxed for 6 h. After removement of the solvent under reduced pressure, the residues were recrystallized from chloroform/petroleum ether to give the corresponding products.

5-Cyano-2-dimethylamino-4-(dimethylamino)azomethino-6-(2-hydroxyethoxy)-pyrimidine (7) 74.8%. mp 148-151°C. IR (KBr): 3447 (OH); 2203 (CN); 1627, 1579, 1507 (C=C, C=N); 1452, 1420; 1289 (C-N); 1105, 1082 (C-O). ^{1}H-NMR (300 MHz, $CDCl_3$): δ= 3.16 (s, 12H, 2xN(CH_3)$_2$); 3.94 (m, 2H, CH_2OH); 4.51 (m, 2H, CH_2O); 8.63 (s, 1H, N=C**H**-N). ^{13}C-NMR (75.43 MHz, $CDCl_3$): δ= 35.0, 37.0, 41.1 (-, 3s, 2xN(CH_3)$_2$); 61.5 (+, CH_2OH); 68.5 (+, CH_2O); 74.0 (+, C-5); 116.8 (+, **C**N); 156.6 (-, N=**C**H-N); 160.4 (+, C-2); 170.4 (+, C-4). MS m/z (%): [M+1]$^+$: 279 (14); M$^+$: 278 (93); 234 (27); 219 (51); 205 (18); 190 (15); 178 (13); 122 (15); 98 (13); 71 (32); 57 (17); 44 (100). HRMS: Calcd for $C_{12}H_{18}N_6O_2$: 278.1491. Found: 278.1491. *Anal.* Calcd for $C_{12}H_{18}N_6O_2$: C, 51.79; H, 6.52; N, 30.20. Found: C, 51.65; H, 6.61; N, 29.62.

5-Cyano-2-dimethylamino-4-(dimethylamino)azomethino-6-ethoxypyrimidine (8) 59.8%. mp 178-182°C. IR (KBr): 2205 (CN); 1630, 1580, 1511 (C=C, C=N); 1487, 1418, 1359; 1320 (C-N); 1081 (C-O). ^{1}H-NMR (250 MHz, $CDCl_3$): δ= 1.39 (t, J= 7.1 Hz, 3H, CH_2CH_3); 3.14 (d, J= 4.4 Hz, 6H, CHN(CH_3)$_2$); 3.16 (s, 6H, N(CH_3)$_2$); 4.42 (q, J= 7.1 Hz, 2H, CH_2O); 8.61 (s, 1H, N=C**H**-N). ^{13}C-NMR (90.56 MHz, $CDCl_3$): δ= 14.45 (-, CH_2CH_3); 34.99 (-, N(CH_3)$_2$); 36.87 (-, NCH_3); 41.09 (-, NCH_3); 62.47 (+, OCH_2); 117.2 (+, **C**N); 156.6 (-, N=**C**H-N); 161.0 (+, C-2); 170.7 (+, C-4); 170.9 (+, C-6). MS m/z (%): [M+1]$^+$: 263 (17); M$^+$: 262 (100); 247 (35); 219 (61); 190 (23); 122 (14), 71 (32); 44 (74). HRMS: Calcd for $C_{12}H_{18}N_6O$: 262.1542. Found: 262.1542. *Anal.* Calcd for $C_{12}H_{18}N_6O$: C, 54.95; H, 6.92; N, 32.04. Found: C, 54.78; H, 6.59; N, 30.57.

General procedure for preparation of 9a-b:

A solution of **6** (0.31 g, 1.5 mmol) and phosgeneiminium salts (**4**) (3 mmol) in 1,2-dichlorethane (20 mL) was refluxed for 4 h. A stream of dry hydrogen chloride was passed the mixture for 3 h under reflux. After cooled to rt, the reaction mixture was allowed to stand overnight. The solvent was removed under reduced pressure and the residue was chromatographed on a silica column (70-230 mesh) using ethyl acetate as eluent to give the products.

5-Cynao-2-dimethylamino-4-(dimethylamino-chloro)azomethino-6-ethoxy-pyrimidine (9a) 42.6%. mp 135°C (ethyl acetate). IR (KBr): 2214 (CN), 1680, 1653, 1593, 1513 (C=C, C=N); 1349, 1255 (C-N); 1077 (C-O). ^{1}H-NMR (360 MHz, $CDCl_3$): δ= 1.42 (t, J= 7.1 Hz, 3H, CH_2CH_3); 3.19 (s, 6H, N(CH_3)$_2$); 3.22 (s, 6H, CClN(CH_3)$_2$); 4.45 (q, J =7.1 Hz, 2H, OCH_2CH_3). ^{13}C-NMR (90.56 MHz, $CDCl_3$): δ= 14.4 (-, CH_2CH_3); 37.1 (-, N(CH_3)$_2$); 40.3 (-, CClN(CH_3)$_2$); 62.9 (+, OCH_2); 74.7 (+, C-5); 116.3 (+, **C**N); 141.2 (+, N=**C**ClN); 161.5 (+, C-2); 169.6 (+, C-4); 170.5 (+, C-6). MS m/z (%): [M+2]$^+$: 298 (35); M$^+$: 296 (100); 261 (47);

260 (20); 245 (52); 217 (76); 173 (18); 71 (96); 44 (48). *Anal.* Calcd for $C_{12}H_{17}N_6OCl$: C, 48.57; H, 5.77; N, 28.32. Found: C, 48.80; H, 5.97; N, 28.16.

4-(Chloropiperidino)azomethino-5-cyano-2-dimethylamino-6-ethoxyprimidine (9b) 19.8%. mp 134-135°C (ethyl acetate). IR (KBr): 2213 (CN); 1669, 1593, 1565, 1512 (C=C, C=N); 1087 (C-O). ^{1}H-NMR (250 MHz, $CDCl_3$): δ= 1.40 (t, J= 7.1 Hz, 3H, CH_2CH_3); 1.68 (s, 6H, -$(CH_2)_3$-); 3.19 (s, 6H, $N(CH_3)_2$); 3.73 (s, 4H, $N(CH_2)_2$); 4.43 (m, J= 7.1 Hz, 2H, OCH_2CH_3). ^{13}C-NMR (90.56 MHz, $CDCl_3$): δ= 14.1 (-, CH_2CH_3); 24.3 (+, C-3´); 25.5 (+, C-1´, 2´); 37.0 (-, d, $N(CH_3)_2$); 62.7 (+, d, CH_2CH_3); 74.9 (+, C-5); 116.2 (+, CN); 140.3 (+, N=CCl N); 161.5 (+, C-4); 169.7 (+, C-2); 170.5 (+, C-6). MS m/z (%): $[M+2]^+$: 338 (33); M^+: 336 (99); 301 (100); 300 (70); 285 (24); 271 (51); 257 (34); 205 (28); 93 (22); 84 (50); 71 (98); 55 (33); 44 (25); 41 (53). HRMS: Calcd for $C_{15}H_{21}N_6OCl$:336.1465. Found: 336.1465. *Anal.* Calcd for $C_{15}H_{21}N_6OCl$: C, 53.49; H, 6.28; N, 24.95. Found: C, 53.11; H, 6.20; N, 25.42.

General procedure for preparation of 10a-b:

A solution of **9** (0.5 mmol) and ammonium hydroxide (30% aq., 6 mL) in ethanol (20 mL) was heated and refluxed for 2 d. After removment of the solvent under reduced pressure, the residue was chromatographed on a silica column (70-230 mesh) using ethyl acetate as eluent to give the products.

4-Amino-2,7-bis(dimethylamino)-5-ethoxypyrimido[4,5-*d*]pyrimidine (10a) 57.2%. mp 205-207°C (acetone/petroleum ether). IR (KBr): 3455, 3327, 3225 (NH); 1597, 1525 (C=N, C=C); 1377, 1336; 1276 (C-N); 1091 (C-O). ^{1}H-NMR (250 MHz, $CDCl_3$): δ= 1.46 (t, J= 7.2 Hz, 3H, CH_2CH_3); 3.21 (s, 6H, $N(CH_3)_2$); 3.23 (s, 6H, $N(CH_3)_2$); 4.53 (q, J= 7.2 Hz, 2H, OCH_2CH_3); 5.6-6.8 (2H, NH_2). ^{13}C-NMR (62.89 MHz, $CDCl_3$): δ= 14.5 (-, CH_2CH_3); 37.0 (-, $N(CH_3)_2$); 83.3 (+, C-4a); 161.3 (+, C-4); 162.3 (+, C-8a); 163.4 (+, C-2); 166.9 (+, C-7); 168.9 (+, C-5). MS m/z (%): $[M+1]^+$: 278 (16); M^+: 277 (100); 262 (51); 248 (22); 234 (77); 205 (23); 125 (12); 71 (41); 44 (17). HRMS: Calcd for $C_{12}H_{19}N_7O$: 227.1652. Found: 277.1653. *Anal.* Calcd for $C_{12}H_{19}N_7O$: C, 51.97; H, 6.91; N, 35.36. Found: C, 51.72; H, 7.15; N, 34.78.

4-Amino-7-dimethylamino-5-ethoxy-2-piperidinopyrimidino[4,5-*d*]pyrimidine (10b) 33.8%. mp 215-218°C (acetone/petroleum ether). IR (KBr): 3467, 3436, 3286 (NH); 1584, 1554, 1517 (C=C, C=N); 1287, 1257 (C-N); 1100 (C-O). ^{1}H-NMR (250 MHz, $CDCl_3$): δ= 1.48 (m, 9H, OCH_2CH_3, -$(CH_2)_3$-); 3.22 (s, 6H, $N(CH_3)_2$); 3.86 (t, J= 5.7 Hz, 4H, -CH_2NCH_2-); 4.54 (m, 2H, OCH_2CH_3); 5.7-6.8 (2H, NH_2). ^{13}C-NMR (62.89 MHz, $CDCl_3$): δ= 14.5 (-, CH_2CH_3); 25.0 (+, C-3´); 26.2 (+, C-2´); 37.1 (-, $N(CH_3)_2$); 44.7 (+, $N(CH_2)_2$); 62.6 (+, OCH_2); 83.4 (+, C-4a); 161.4 (+, C-4); 162.4 (+, C-8a); 163.0 (+, C-2); 166.8 (+, C-7); 169.1 (+, C-5). MS m/z (%): $[M+1]^+$: 318 (19); M^+: 317 (100); 288 (51); 262 (31); 234 (93); 190 (15); 71 (31); 55 (15); 44 (22); 43 (20). HRMS: Calcd for $C_{15}H_{23}N_7O$: 317.1964. Found: 317.1964.

Anal. Calcd for $C_{15}H_{23}N_7O$: C, 56.76; H, 7.30; N, 30.89. Found: C, 55.88; H, 7.39; N, 30.06.

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