Reactions of ethyl 4-amino-6-(ethoxycarbonylmethyl)-2-phenylpyrimidine-5-carboxylate with hydrazines

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New substituted 4,6-diamino-7-hydroxypyrido[4,3-*d*]pyrimidin-5(6*H*)-ones were synthesized by treatment of ethyl 4-amino-6-(ethoxycarbonylmethyl)-2-phenylpyrimidine-5-carboxylic acid with hydrazine hydrate and phenylhydrazine. In the case of methylhydrazine, the reaction proceeded in an unusual way and afforded a product identified, relying on NMR data, as functionally substituted 8-(5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-7-ylidene)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine comprising two amineimide fragments. A diacetyl derivative of this compound was obtained.

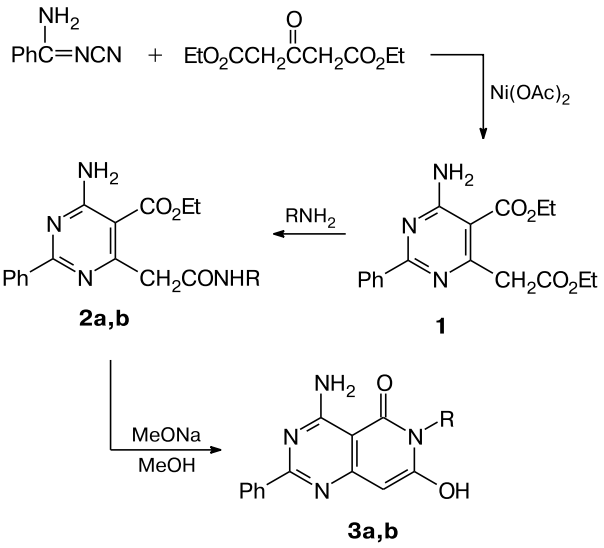
Key words: ethyl 4-amino-6-(ethoxycarbonylmethyl)-2-phenylpyrimidine-5-carboxylate, hydrazines, substituted pyrido[4,3-*d*]pyrimidines, heterocyclization.

Substituted 4-aminopyrido[4,3-*d*]pyrimidines inhibit tyrosine kinase,[1] and pyrido[4,3-*d*]pyrimidin-5(6*H*)-one derivatives exhibit antihypertensive,[2] antiallergic,[3] and herbicidal[4] activities. Our interest was in the development of new versions of the synthesis of pyrido[4,3-*d*]pyrimidin-5-ones containing an amino group.

In the previous paper,[5] we reported that ethyl 4-amino-6-(ethoxycarbonylmethyl)-2-phenylpyrimidine-5-carboxylate (**1**), obtained from *N*-cyanobenzamidine and diethyl acetone-1,3-dicarboxylate in the presence of $Ni(OAc)_2$, is converted, under the treatment by primary amines, into amides **2,** which cyclize under the treatment by MeONa in MeOH to give pyrido[4,3-*d*]pyrimidin-5-one derivatives **3** (Scheme 1).

In continuation of this work, we studied the reactions of diester **1** with hydrazines. We found that refluxing of diester **1** with a large excess of phenylhydrazine in *p*-xylene affords diaminopyrido[4,3-*d*]pyrimidin-5-one **4** similar in structure to compounds **3** (Scheme 2). Apparently, hydrazide **5** is formed intermediately; however, under the reaction conditions, it is converted into bicyclic product **4** as a result of intramolecular condensation. The ^{1}H NMR spectrum (DMSO-d_6) of this product shows a singlet at 5.42 ppm (H(8)) and a broad singlet centered at 12.22 ppm for the OH group (*cf.* signals at 5.39 and 12.18 ppm for compound **3a**). These data do not contradict the pyridopyrimidine structure of **4** and do not correspond to the alternative pyrimidodiazepine structure **6**. The mass spectrum of compound **4** shows a molecular ion peak and the IR spectrum exhibits a carbonyl absorption band at 1680 cm^{-1}.

Scheme 1



R = $PhCH_2$ (**a**), Bu (**b**)

The reaction of diester **1** with a large excess of hydrazine hydrate in boiling butanol also yields pyrido[4,3-*d*]-pyrimidin-5-one but in this case, the process is accompanied by replacement of the NH_2 group by hydrazine. Compound **7** thus obtained was then converted into diacetyl derivative **8** by treatment with excess Ac_2O in boiling benzene (Scheme 3).

The structures of compounds **7** and **8** were confirmed by spectral methods. The mass spectra of these compounds

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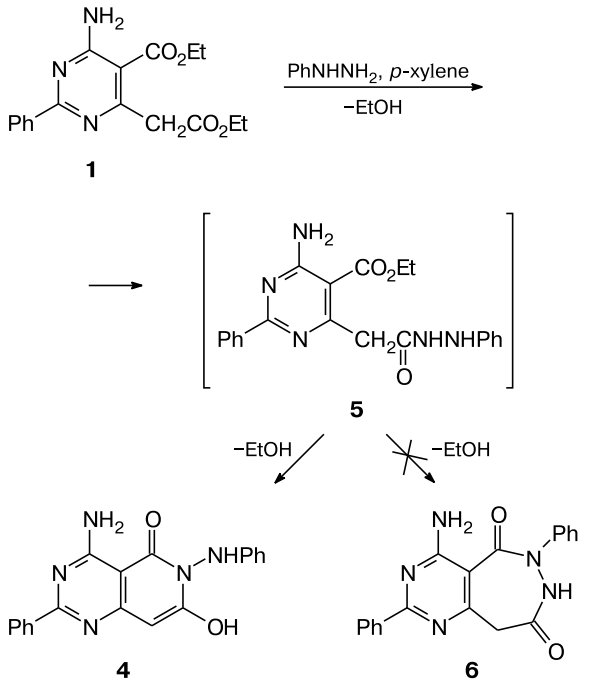
Scheme 2

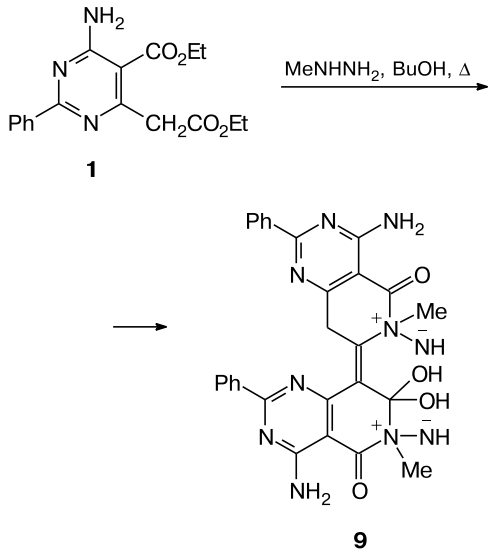


show strong molecular ion peaks. The ^{1}H NMR spectra (DMSO-d_6), like the spectra of compounds **3** and **4**, exhibit a singlet at 5.42—5.45 ppm (H(8)). The spectrum of compound **7** has a broadened singlet at 10.88 ppm (NH) and a very broad singlet in the range of 5.0—5.8 ppm from two NH_2 groups. The spectrum of heterocycle **8** exhibits three broadened singlets at 10.78 (NH), 10.10, and 11.39 ppm (2 NHCO).

The reaction of diester **1** with methylhydrazine proceeds in an unusual way. Long-term refluxing of compound **1** with a large excess of methylhydrazine in butanol gave a yellow solid poorly soluble in organic solvents, and its structure was obviously different from that of the above described pyridopyrimidines **3**, **4**, and **7**. Detailed investigation of the product by NMR and mass spectrometry together with elemental analysis data point to structure **9** (Scheme 4).

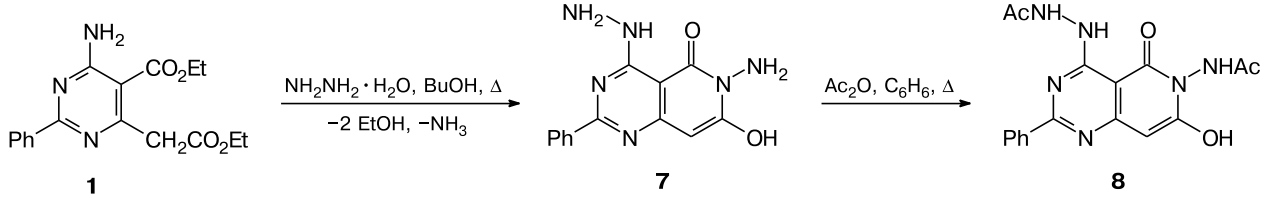
Thus the ^{1}H NMR spectrum (DMSO-d_6) of compound **9** does not show the singlet at 5.33—5.45 ppm (CH), which is present in the spectra of heterocycles **3**, **4**,

Scheme 4



and **7**, but contains three closely located singlets with different intensity (3.81, 3.82, and 3.84 ppm), which correlate with the carbon signal at 18.9 ppm in the 2D {^{1}H—^{13}C} HSQC NMR spectra. Analysis of the GATED and APT[6] ^{13}C NMR spectra shows that this signal is related to the CH_2 group. The integral intensity ratio of the ^{1}H NMR signals of CH_2 protons to the rest protons corresponds to structure **9**, which is formally the product of condensation of two pyridopyrimidine molecules involving the CH_2 group of one molecule and the carbonyl group of the other molecule. Indeed, the {^{1}H—^{13}C} HMBC 2D NMR spectrum of compound **9** recorded in a mixture of CF_3COOH and DMSO-d_6 shows a correlation of CH_2 protons with four carbon atoms: 95.2 ppm. (C(4a′)), 142.8, 143.6 ppm (C(7′) and C(8)) and 162.5 ppm (C(8a′)), which confirms the presence of a double bond between the carbon atoms (C(7′) and C(8)) connecting two bicyclic fragments. In turn, the unusually high-field ^{13}C NMR chemical shift (18.9 ppm) for a CH_2 group connected to the electron-withdrawing pyrimidine ring (for example, for pyrimidine **1**, the CH_2-group signal is observed at 45.7 ppm), which suggests that this molecule incorporates fragments with oppositely charged nitrogen atoms.

Scheme 3



In the ^{1}H NMR spectrum of heterocycle **9**, as in spectra of bicyclic compounds **3** and **4**, the signals for NH_2 groups are observed as two broadened singlets at 8.83 and 9.52 ppm and the chemical shifts of the Ph protons of all of these compounds are similar. In addition, compound **9** has two OH groups (four closely located relatively narrow singlets at 13.43, 13.50, 13.54, and 13.59 ppm with two-proton total intensity)* and two NH groups (broad singlet at 5.6—6.2 ppm) whose protons do not show correlation with the carbon atoms in the HSQC 2D spectrum. The signals of the NMe groups in the ^{1}H NMR spectrum overlap with the DMSO signal, which is confirmed by correlation of these protons with the carbon at 36.3 ppm in the HSQC 2D spectrum. The {^{1}H—^{1}H} COSY 2D spectrum shows correlation only between the Ph group protons and between the NH_2 group protons, which confirms the singlet character of the CH_2-group signals and points to the absence of the MeNH fragment.

The fact that the ^{1}H NMR spectrum of compound **9** exhibits three signals with 1 : 2 : 1 ratio for the CH_2 group and four signals for the OH group is explained by the presence of two asymmetric centers (tetrahedral positively charged nitrogen atoms) in the molecule, resulting in the possible formation of four stereoisomers (RR, SR and RS, SS).

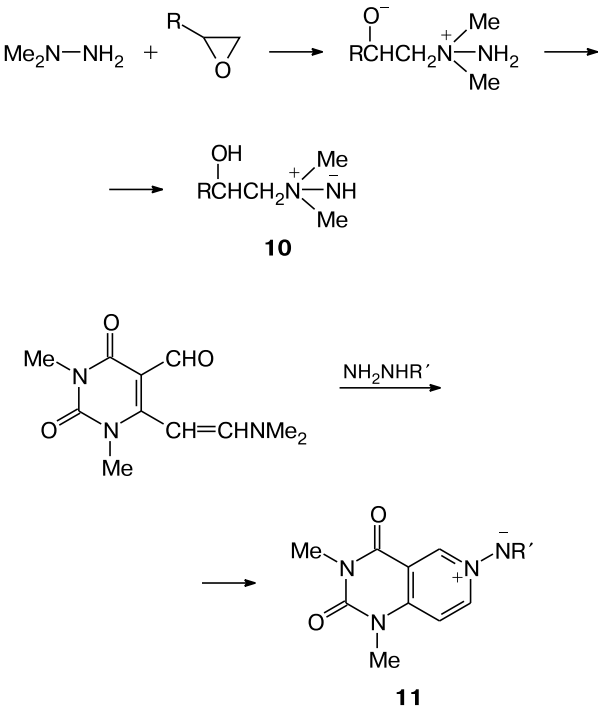
The EI mass spectrum of heterocycle **9** does not show a molecular ion peak (fragmentation is presented in the Experimental); however, the MALDI mass spectrum contains an intensive ion peak at 567 $[M + H]^+$. The IR spectrum of compound **9** in KBr exhibits only one carbonyl absorption band (1656 cm^{-1}), which is also in line with the assumed structure.

1,1-Dimethylhydrazine is known[7] to react with epoxides by more nucleophilic nitrogen to give amineimides **10**. In addition, the reaction of 1,3-dimethyl-6-dimethylaminovinyl-5-formyluracils with hydrazines affords the corresponding products **11** (Scheme 5)[8].

All this suggests that the reaction of diester **1** with methylhydrazine occurs according to Scheme 6.

Apparently, methylhydrazine first reacts with diester **1** by more nucleophilic MeNH fragment to give hydrazide **12**, which cyclizes to give not pyrimidodiazepine **13** but pyridopyrimidine **14**. The subsequent proton transfer from the NH_2 group to the negatively charged oxygen atom and elimination of EtOH affords pyridopyrimidine **16** where the electrophilicity of carbonyl groups is enhanced due to the presence of positive charge on the endocyclic nitrogen atom. This promotes condensation of two molecules of this bicyclic compound to give compound **17**. The subsequent hydration of this intermediate leads to heterocycle **9**.

Scheme 5



R′ = H, Me, Ac

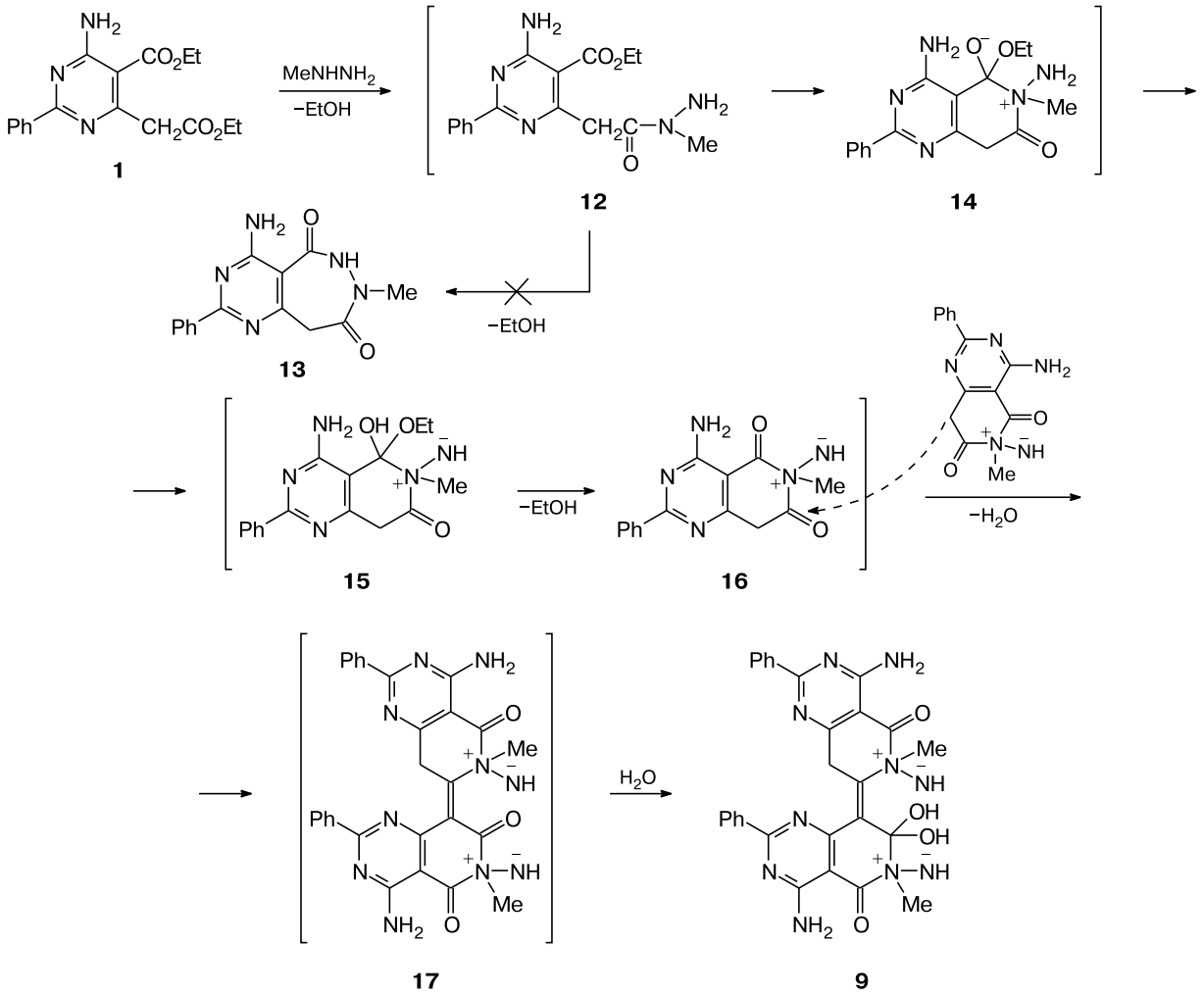
It is known[7] that amineimides are readily acylated at the imide nitrogen; therefore, we studied the reactions of compound **9** with acid anhydrides. Refluxing of heterocycle **9** with excess Ac_2O in toluene gave a yellow precipitate of compound **18** (Scheme 7). Treatment of more bulky isobutyric anhydride does not give acylated product for steric reasons, the initial heterocycle being recovered unchanged.

The structure of compound **18** is confirmed by spectral data. The MALDI mass spectrum of this heterocycle exhibits an intense ion peak at 651 $[M + H]^+$, while the IR spectrum (KBr), like that of the initial compound **9**, exhibits only one absorption band for carbonyl groups at 1668 cm^{-1}, while absorption below 1600 cm^{-1} is typical of carbonyl groups of acylhydrazinium compounds.[7]

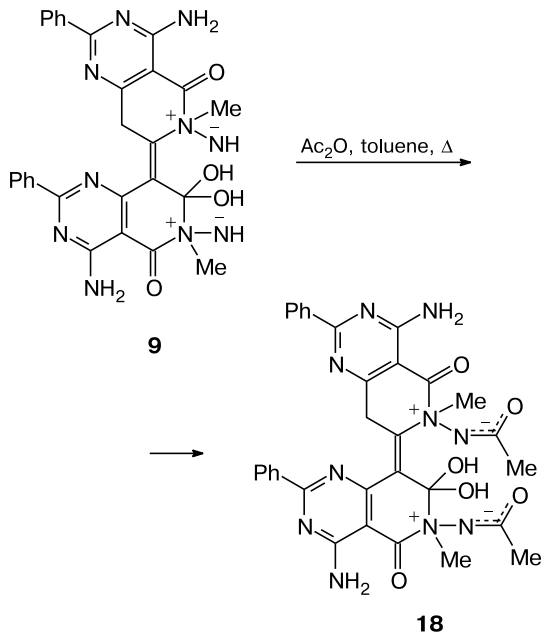
In comparison with the ^{1}H NMR spectrum (DMSO-d_6) of the starting compound **9**, the spectrum of the diacetyl derivative **18** does not exhibit signals at 4.0—7.0 ppm, while three singlets at ~3.8 ppm (CH_2) are retained, broad singlets for two acetyl groups appear (1.65 and 1.91 ppm), and the signal of NMe groups (2.97 ppm) is broadened. In addition, as opposed to the spectrum of the initial compound **9**, this spectrum exhibits a double set of signals for NH_2 groups (8.82 and 9.38 ppm, 8.98 and 9.38 ppm), which is confirmed by correlation of these proton couples with each other in the COSY 2D spectrum. Also it should be noted that the signal of the OH group at 13.1 ppm becomes very broad (now its intensity corresponds to one

* Low-field chemical shifts correspond to hydrogen bond between the hydroxyl protons and negatively charged nitrogen atoms and are thus indicative of the *Z*-configuration of compound **9**.

Scheme 6



Scheme 7



proton) and the other OH group is manifested as a broadened singlet at 10.2 ppm. In the ^{1}H NMR spectrum (DMSO-d_6) recorded at 100 °C, the COMe and NMe group signals narrow down and the OH signal at 13.1 ppm narrows down to a greater extent, which indicates the hindrance of rotation around the C—N bond of the amide fragment. The ^{13}C NMR spectrum of heterocycle **18** shows signals for two COMe groups (19.3 and 20.2 ppm), a signal for the NMe group (33.5 ppm), and a broad signal at 18.9 ppm, which corresponds to the CH_2 group according to the APT ^{13}C NMR spectrum.

Thus, the results presented in this work demonstrate that in reactions with hydrazine and its monosubstituted derivatives, diester **1** tends to form a pyridine rather than a diazepine ring. Note in this connection that the compounds synthesized from homophthalic anhydride or methyl 1-methyl-2-(methoxycarbonylmethyl)indole-3-carboxylate and hydrazine hydrate were initially believed to be fused diazepines.[9,10] However, the subsequent studies[11,12] showed that in these cases, too, it is the pyridine ring that is annulated.

Experimental

^{1}H NMR spectra were recorded on Bruker AM-300 and Bruker DRX-500 instruments and ^{13}C NMR and {^{1}H—^{1}H} COSY and {^{1}H—^{13}C} HSQC and HMBC 2D NMR spectra were measured on a Bruker DRX-500 spectrometer in DMSO-d_6. IR spectra (KBr pellets) were measured on a Specord-M82 instrument and mass spectra were run on a Kratos MS-30 mass spectrometer (EI, 70 eV, ionization chamber at 250 °C, direct sample injection) and REFLEX III Bruker Daltonics mass spectrometer (MALDI TOF MS, positive ion mode, 2,5-dihydroxybenzoic acid or 2-amino-4-methyl-5-nitropyridine as the matrix).

Diester **1** was synthesized by a known procedure.[5] ^{13}C NMR ($CDCl_3$), δ: 14.1 (Me); 14.2 (Me); 45.7 (CH_2); 60.8 (CH_2O); 61.4 (CH_2O); 102.9 (C(5)); 128.3 (*m*-CH, Ph); 128.7 (*o*-CH, Ph); 131.1 (*p*-CH, Ph); 136.9 (*ipso*-C, Ph); 164.1 (C(4)); 164.5 (C(2)); 165.1 (C(6)); 167.0 (CO); 170.1 ($CH_2\underline{C}O$) (the signals were assigned using HSQC and HMBC 2D spectra).

All of the prepared compounds were poorly soluble in organic solvents and were isolated in analytically pure form without recrystallization.

4-Amino-7-hydroxy-2-phenyl-6-phenylaminopyrido[4,3-*d*]-pyrimidine-5(6*H*)-one (4). A mixture of diester **1** (0.165 g, 0.5 mmol) and phenylhydrazine (0.50 mL, 5 mmol) in *p*-xylene (4 mL) was refluxed for 12 h and cooled to 20 °C, and the precipitate was filtered off and washed with petroleum ether to give 0.047 g (27%) of compound **4**, m.p. > 350 °C. Found (%): C, 65.75; H, 4.23; N, 20.03. $C_{19}H_{15}N_5O_2$. Calculated (%): C, 66.08; H, 4.38; N, 20.28. MS, *m/z* (I_{rel} (%)): 345 $[M]^+$ (45), 254 $[M - PhN]^+$ (83), 238 $[M - PhNHNH]^+$ (29), 211 $[M - PhNHNCO]^+$ (41), 104 $[PhC{=}NH]^+$ (50), 93 (100). IR, ν/cm^{-1}: 3312 (NH), 3200—3000 (NH, CH), 1680 (CO), 1604, 1588, 1512. ^{1}H NMR, δ: 5.42 (s, 1 H, H(8)); 6.57 (d, 2 H, *o*-H, PhN, J = 7.5 Hz); 6.71 (t, 1 H, *p*-H, PhN, J = 7.5 Hz); 7.12 (t, 2 H, *m*-H, PhN, J = 7.5 Hz); 7.65 (m, 3 H, Ph); 8.11 (m, 2 H, Ph); 8.13 (br.s, 1 H, NH); 8.63, 9.30 (both br.s, 1 H each, NH_2); 12.22 (br.s, 1 H, OH).

6-Amino-4-hydrazino-7-hydroxy-2-phenylpyrido[4,3-*d*]-pyrimidin-5(6*H*)-one (7). A mixture of diester **1** (0.197 g, 0.6 mmol) and hydrazine hydrate (1.1 mL, 21 mmol) in BuOH (4 mL) was refluxed for 3 h, butanol and excess hydrazine were removed *in vacuo*, MeOH (10 mL) was added to the residue, the mixture was heated to boiling, and the insoluble precipitate was filtered off to give 0.11 g (67%) of compound **7**, m.p. > 350 °C. Found (%): C, 54.72; H, 3.90; N, 29.14. $C_{13}H_{12}N_6O_2$. Calculated (%): C, 54.92; H, 4.25; N, 29.56. MS, *m/z* (I_{rel} (%)): 284 $[M]^+$ (100), 269 $[M - NH]^+$ (75), 254 $[M - NH_2N]^+$ (89), 253 $[M - NH_2NH]^+$ (94), 238 $[M - NH_2N - NH_2]^+$ (56), 104 $[PhC{=}NH]^+$ (89). IR, ν/cm^{-1}: 3324 (NH), 3232 (NH), 1666 (CO), 1624, 1608, 1560, 1540. ^{1}H NMR, δ: 5.00—5.80 (br.s, 4 H, 2 NH_2); 5.45 (s, 1 H, H(8)); 7.62 (m, 3 H, Ph); 8.26 (m, 2 H, Ph); 10.88 (br.s, 1 H, NH).

6-Acetylamino-4-(2-acetylhydrazino)-7-hydroxy-2-phenylpyrido[4,3-*d*]pyrimidin-5(6*H*)-one (8). A mixture of pyridopyrimidinone **7** (0.142 g, 0.5 mmol) and acetic anhydride (0.20 mL, 2.1 mmol) in anhydrous benzene (5 mL) was refluxed for 2 h and cooled to 20 °C, the precipitate was filtered off and washed with petroleum ether to give 0.14 g (77%) of compound **8**, m.p. 336—340 °C (dec.). Found (%): C, 55.12; H, 4.21; N, 22.58. $C_{17}H_{16}N_6O_4$. Calculated (%): C, 55.43; H, 4.38; N, 22.82. MS, *m/z* (I_{rel} (%)): 368 $[M]^+$ (30), 326 $[M - COCH_2]^+$ (52), 284 $[M - 2\,COCH_2]^+$ (100), 269 $[M - COCH_2 - MeCON]^+$ (95), 254 $[M - COCH_2 - MeCONHN]^+$ (53), 253 $[M - COCH_2 - MeCONHNH]^+$ (52), 226 $[M - COCH_2 - MeCONHNCO]^+$ (35), 104 $[PhC{=}NH]^+$ (62). IR, ν/cm^{-1}: 3230 (NH), 1688 (CO), 1664 (CO), 1624, 1560, 1524. ^{1}H NMR, δ: 2.00 (s, 3 H, COMe); 2.05 (s, 3 H, COMe); 5.42 (s, 1 H, H(8)); 7.62 (m, 3 H, Ph); 8.20 (m, 2 H, Ph); 10.10 (br.s, 1 H, NHCO); 10.78 (br.s, 1 H, NH); 11.39 (br.s, 1 H, NHCO); 12.49 (br.s, 1 H, OH).

4-Amino-8-(4-amino-6-imido-6-methyl-5-oxo-2-phenyl-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-7-ylidene)-7,7-dihydroxy-6-methyl-5-oxo-2-phenyl-5,6,7,8-tetrahydropyrido[4,3-*d*]-pyrimidine 6-imide (9). A mixture of diester **1** (0.24 g, 0.73 mmol) and methylhydrazine (1.6 mL, 30 mmol) in BuOH (4 mL) was refluxed for 12 h and cooled to 20 °C, and the precipitate was filtered off and washed with MeOH (5 mL) to give 0.10 g (48%) of compound **9**, m.p. > 350 °C. Found (%): C, 58.92; H, 4.66; N, 24.39. $C_{28}H_{26}N_{10}O_4$. Calculated (%): C, 59.36; H, 4.63; N, 24.72. MS MALDI, *m/z*: 567 $[M + H]^+$. MS EI, *m/z* (I_{rel} (%)): 281 $[A - H_2O]^+$ (41), 269 $[A - MeNH]^+$ (52), 267 $[B]^+$ (16), 266 $[B - H]^+$ (29), 254 $[A - MeNNH_2]^+$ (40), 238 $[B - MeN]^+$ (87), 211 $[A - MeNHNCO - H_2O + H_2]^+$ (35), 195 $[B - MeNHNCO]^+$ (21), 104 $[PhC{=}NH]^+$ (100), where A and B are fragments obtained upon cleavage of the bond connecting the bicyclic moieties, their weights are 299 and 267, respectively. IR, ν/cm^{-1}: 3276, 3132, 1656 (CO), 1624, 1568, 1540, 1520. ^{1}H NMR, δ: 2.50 (s, 6 H, 2 NMe); 3.81, 3.82, 3.84 (all s, 2 H, CH_2); 5.60—6.20 (br.s, 2 H, 2 NH); 7.70 (m, 6 H, *m*-H, *p*-H, 2 Ph); 8.41 (m, 4 H, *o*-H, 2 Ph); 8.83, 9.52 (both br.s, 4 H, 2 NH_2); 13.43, 13.50, 13.54, 13.59 (all s, 2 H, 2 OH). ^{13}C NMR, δ: 18.9 (t, CH_2, ^1J = 127.0 Hz); 36.3 (q, 2 NMe, ^1J = 136.0 Hz); 86.1, 92.4 (C(4a), C(4a′), C(7)); 128.4 (d, *o*-CH, 2 Ph, *m*-CH, 2 Ph, ^1J = 162.8 Hz); 131.3 (*ipso*-C, 2 Ph); 132.6 (d, *p*-CH, 2 Ph, ^1J = 164.6 Hz); 140.5, 142.3 (C(7′), C(8)); 157.2, 157.9, 159.4, 161.3, 161.7 (C(2), C(2′), C(4), C(4′), C(8a), C(8a′)); 182.5 (C(5), C(5′)).

4-Amino-8-(6-acetylimido-4-amino-6-methyl-5-oxo-2-phenyl-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-7-ylidene)-7,7-dihydroxy-6-methyl-5-oxo-2-phenyl-5,6,7,8-tetrahydropyrido[4,3-*d*]-pyrimidine 6-acetylimide (18). A mixture of compound **9** (0.142 g, 0.5 mmol) and acetic anhydride (1.6 mL, 17 mmol) in toluene (10 mL) was refluxed for 4 h and cooled to 20 °C, and the precipitate was filtered off and washed with petroleum ether to give 0.14 g (87%) of compound **18**, m.p. > 350 °C. Found (%): C, 58.66; H, 4.35; N, 21.24. $C_{32}H_{30}N_{10}O_6$. Calculated (%): C, 59.07; H, 4.65; N, 21.53. MS MALDI, *m/z*: 651 $[M + H]^+$. IR, ν/cm^{-1}: 3356, 3288, 3212, 1668 (CO), 1628, 1568, 1560, 1516. ^{1}H NMR, δ: 1.65, 1.91 (both br.s, 6 H, 2 COMe); 2.97 (br.s, 6 H, 2 NMe); 3.77, 3.80, 3.82 (all s, 2 H, CH_2); 7.70 (m, 6 H, *m*-H, *p*-H, 2 Ph); 8.35 (m, 4 H, *o*-H, 2 Ph); 8.82, 8.98, 9.38 (all br.s, 4 H, 2 NH_2); 10.21, 13.10 (both br.s, 2 H, 2 OH). ^{13}C NMR, δ: 18.9 (CH_2); 19.3 (q, CO<u>Me</u>, ^1J = 130 Hz); 20.2 (q, CO<u>Me</u>, ^1J = 129 Hz); 33.5 (q, 2 NMe, ^1J = 146.5 Hz); 86.3, 86.7, 92.0, 92.3, 92.7 (C(4a), C(4a′), C(7)); 128.5 (d, *o*-CH, 2 Ph, *m*-CH, 2 Ph, ^1J = 162.5 Hz); 131.4 (*ipso*-C, 2 Ph); 132.9 (d, *p*-CH, 2 Ph, ^1J = 166.6 Hz); 145.7, 146.5 (C(7′), C(8)); 158.6, 158.9, 160.2, 160.7, 161.8, 163.7, 164.2, 167.8, 170.9 (C(2), C(2′), C(4), C(4′), C(5), C(5′), C(8a), C(8a′), 2 <u>CO</u>Me).

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