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SYNTHESIS AND TRANSFORMATIONS OF PYRIDO[4,3-*d*]-PYRIMIDINES WITH *N*-HETEROCYCLES MOIETIES

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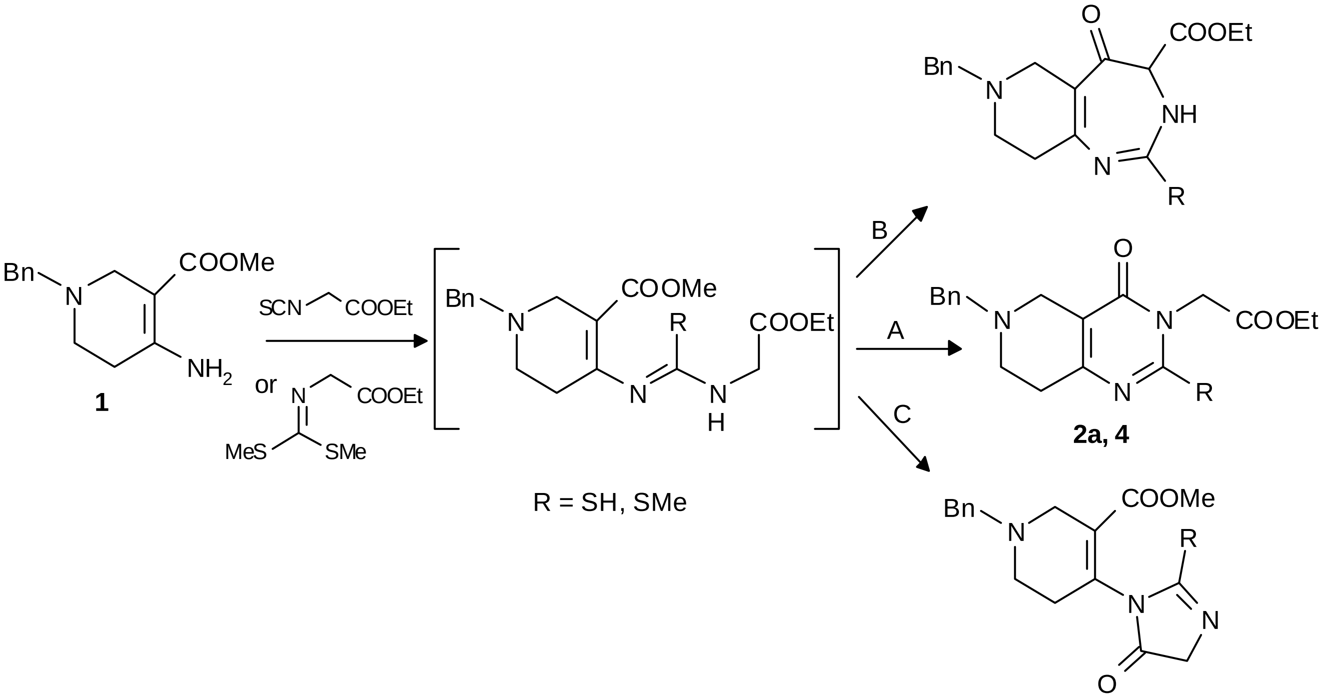
Abstract - *ortho*-Amino ester **(1)** was cyclized to fused pyrimidines by reacting with isocyanate, isothiocyanate, or dithioketal reagent. Thioxo compound **(2a)** was halogenated, methylated and subsequently displaced by amines. *ortho*-Amino ester **(1)** was also converted into directly tricyclic azolopyrido[4,3-*d*]pyrimidines **(8-13)**.

Derivatives of pyrido[2,3-*d*]pyrimidine system are of great interest of its dihydrofolate reductase inhibiting, antibacterial,[1,2] antitumor[3] and antiepileptic activities.[4] Since the direct introduction of some substituents into the pyrimidine ring is not easy, syntheses directed to the construction of the ring bearing useful functional grous in the first step have been well developed.[5] Imidazo[1,2-*a*]pyrido[2,3-*d*]-pyrimidine system has already been synthesized earlier in different research group utilizing multi-step approaches[6,7] different to the method reported in this paper. Here, we report a simple, one-pot reaction for the synthesis of pyrido[4,3-*d*]pyrimidine, imidazo[1,2-*a*]pyrido[4,3-*d*]pyrimidine, pyrimido[1,2-*a*]-pyrido[4,3-*d*]pyrimidine, thiazolo[3,2-*a*]pyrido[4,3-*d*]pyrimidine, pyrido[4',3':4,5]pyrimido[2,1-*b*][1,3]-thiazine and pyrazino[1,2-*a*]-pyrido[4,3-*d*]pyrimidine.

Reaction of *ortho*-amino ester **(1)** with ethyl isothiocyanatoacetate in pyridine or ethyl *N*-[bis-(methylthio)methylene]glycinate (BMMA-reagent) in acetic acid at reflux temperature gave high yields of monoannelated products **(2a, 4)** in one-pot reaction.

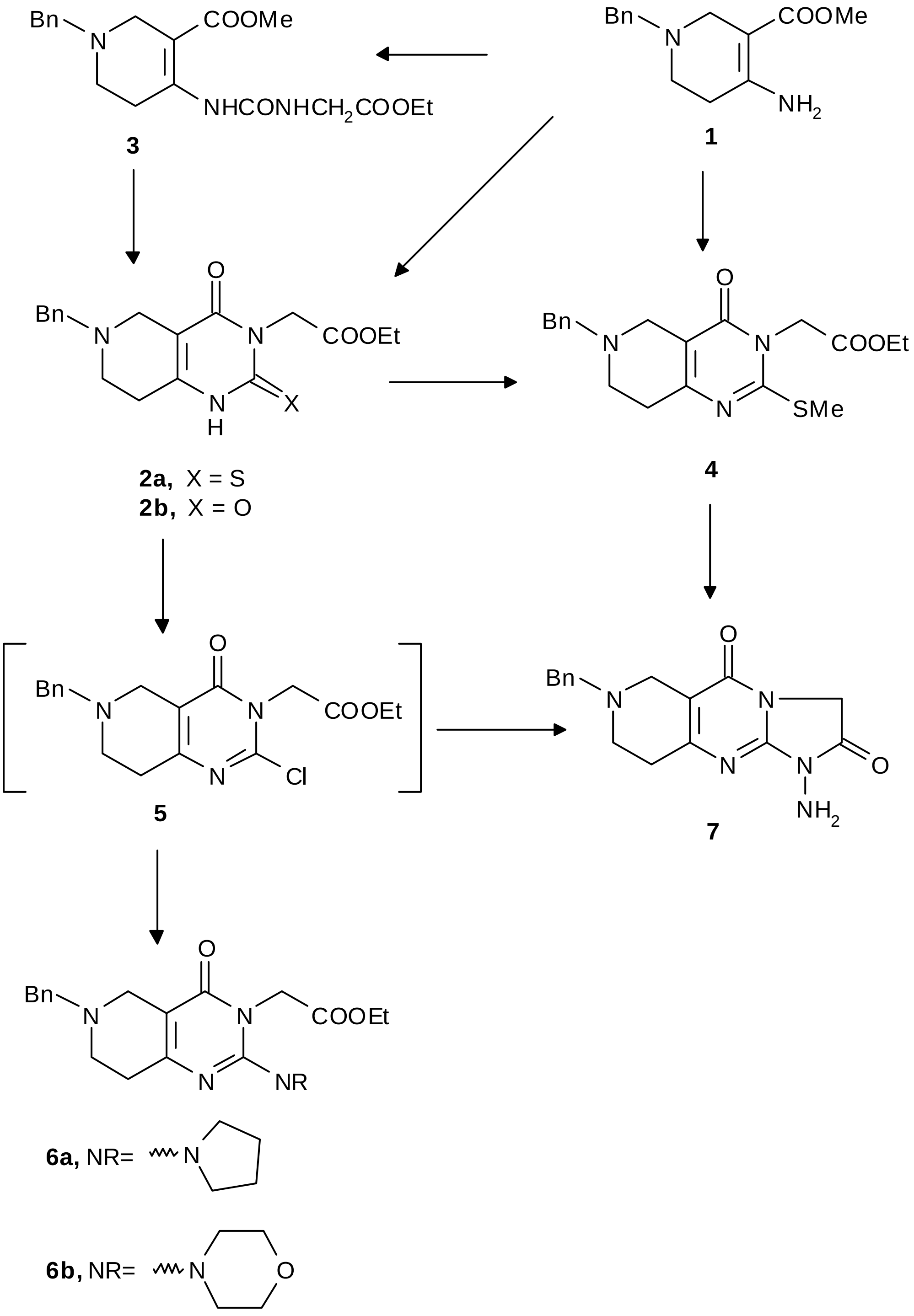
As the cyclization obviously proceeded *via* thiourea intermediate, three possible products of the cyclization had to be considered as shown in Scheme 1. As the undesired but conceivable pathways **B** and **C** (could be formed diazepine derivative or imidazo derivative) could be ruled out by NMR spectroscopy, the method proved to be useful for giving smooth access *via* pathway **A** to pyrido[4,3-*d*]pyrimidine system as depicted by the formulas **(2a, 4)**.



Scheme 1

Thus, methyl 4-amino-1-benzyl-1,2,5,6-tetrahydropyridine-3-carboxylate **(1)** was converted into ethyl 6-benzyl-3,4,5,6,7,8-hexahydro-2-methylthio-4-oxopyrido[4,3-*d*]pyrimidine-3-acetate **(4)**. As depicted in Scheme 2, the intermediate **(4)** can be obtained by the following two sequences: 1) preparation of the thioxopyrimidine **(2a)** by reaction of **1** with ethyl isothiocyanatoacetate, followed by *S*-methylation with methyl iodide, or 2) by the condensation reaction of ethyl *N*-[bis(methylthio)methylene]glycinate with **1** in the presence of acetic acid. Treatment of *ortho*-amino ester **(1)** with ethyl isocyanatoacetate in the presence of pyridine afforded urethane **(3)**, which was cyclized to **2b** with NaOEt.

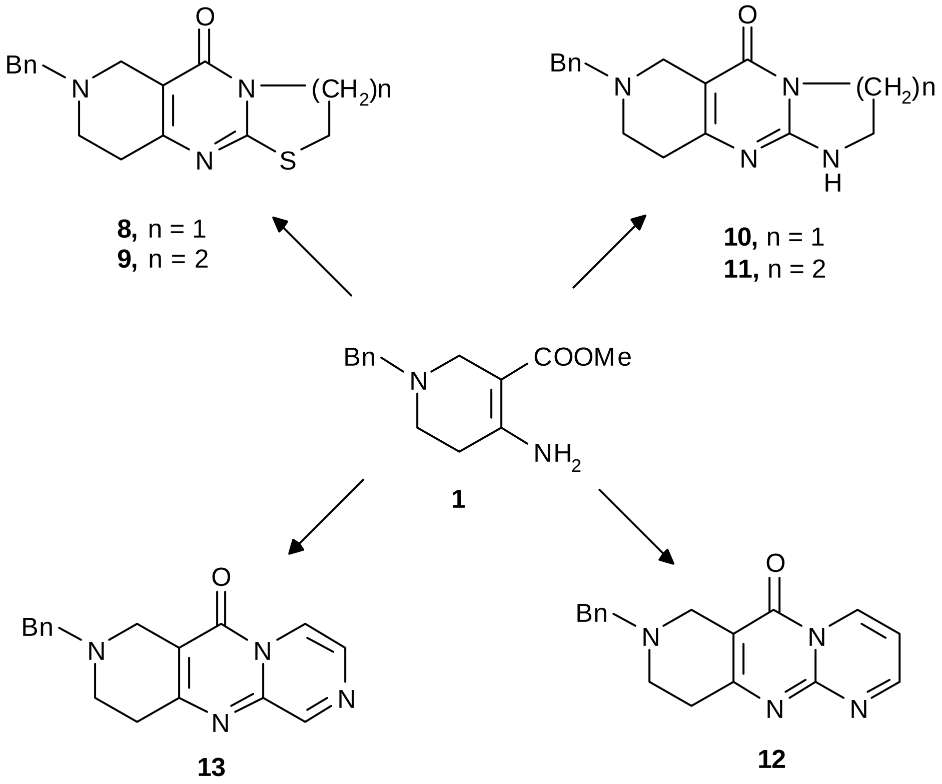
Another key intermediate, chloropyrido[4,3-*d*]pyrimidine derivative **(5)**, was obtained from thioxopyrimidine **(2a)** and $POCl_3$. A substitution reaction of chloro derivative **(5)** with pyrrolidine or morpholine furnished pyrido[4,3-*d*]pyrimidine derivatives **(6)**. On reaction with hydrazine hydrate, chloropyrido[4,3-*d*]pyrimidine derivative **(5)** or the methyl thioester **(4)** afforded the *N*-aminolactam, imidazo[1,2-*a*]pyrido[4,3-*d*]pyrimidine **(7)**.



Scheme 2

A series of imino thioacetals: 2-methylthio-2-thiazoline, 5,6-dihydro-2-methylthio-4*H*-1,3-thiazine, 2-methylthio-2-imidazoline, 2-methylthio-1,4,5,6-tetrahydropyrimidine and 2-methylthio-2-pyrazine, reacted readily with *ortho*-amino ester **(1)** to give the tricyclic fused products, thiazolo[3,2-*a*]pyrido[4,3-*d*]pyrimidine derivative **(8)**, pyrido[4',3':4,5]pyrimido[2,1-*b*][1,3]thiazine derivative **(9)**, imidazo[1,2-*a*]-pyrido[4,3-*d*]pyrimidine derivative **(10)**, pyrido[4,3-*d*]pyrimido[1,2-*a*]pyrimidine derivative **(11)** and pyrazino[1,2-*a*]pyrido[4,3-*d*]pyrimidine derivative **(13)** respectively by an one-step reaction. 2-

Chloropyrimidine also reacted with **1** in one-pot reaction to afford 8-benzyl-7,8,9,10-tetrahydro-6*H*-pyrido[4,3-*d*]pyrimido[1,2-*a*]pyrimidine-6-one **(12)** (Scheme 3).



Scheme 3

EXPERIMENTAL

Melting points were determined on a Yanaco hot stage apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a JNM - ALPHA 500 (500 MHz) spectrometer in $CDCl_3$ or DMSO-d_6 using TMS as internal standard and the chemical shifts are expressed in δ ppm. Elemental analyses were performed on a EA 1108 (Fisons Instruments) Elemental Analyzer.

Using same methods of Sauter *et al.* ethyl *N*-[bis(methylthio)methylene]glycinate[8] and ethyl isothiocyanatoacetate[9] were obtained both as a syrup. 2-Methylthio-2-thiazoline[10,11] and 5,6-dihydro-2-methylthio-4*H*-1,3-thiazine[10,12] were synthesized *via* a two-step procedure from 2-aminoethanol or 3-aminopropanol and CS_2 and subsequent methylation with methyl iodide. 2-Methylthio-2-imidazoline and 2-methylthio-1,4,5,6-tetrahydropyrimidine were prepared according to literature procedures.[13,14] Methyl 4-amino-1-benzyl-1,2,5,6-tetrahydropyridine-3-carboxylate was purchased from Kanto Chemicals. Ethyl isocyanatoacetate, 2-chloropyrimidine and 2-methylthio-2-pyrazine were purchased from Aldrich.

Ethyl 6-benzyl-1,2,3,4,5,6,7,8-octahydro-4-oxo-2-thioxopyrido[4,3-*d*]pyrimidine-3-acetate (2a): A solution of methyl 4-amino-1-benzyl-1,2,5,6-tetrahydropyridine-3-carboxylate **(1)** (0.98 g, 4 mmol) and ethyl isothiocyanatoacetate (0.58 g, 4 mmol) in pyridine (7 mL) was refluxed for 4 h. The reaction mixture was diluted with ethanol and cooled. The resulting crystals were collected by filtration and recrystallized from ethanol to give **2a** as brown needles. Yield: 1.17 g (82%); mp 188-189 ^{0}C. ^{1}H NMR ($CDCl_3$): δ_H 1.19-1.21 (t, *J* = 7.10 Hz, 3H, Me), 2.46 (t, 2H, *J* = 5.19 Hz, 8-H), 2.61 (t, *J* = 5.49 Hz, 2H, 7-H), 3.27 (s, 2H, 5-H), 3.61 (s, 2H, Ph-CH_2), 4.12-4.16 (q, *J* = 7.02 Hz, 2H, OCH_2), 5.07 (s, 2H, CH_2), 7.18-7.35 (m, 5H, Ar-H), 10.80 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ_C 14.04 (q, Me), 26.38 (t, C-8), 47.07 (t, C-7), 47.63 (t, C-5), 48.56 (t, CH_2), 61.62 (t, Ph-CH_2), 61.88 (t, OCH_2), 110.87 (s, C-4a), 127.37 (d, C-4'), 128.92 (d, C-3' and C-5'), 129.69 (d, C-2' and C-6'), 137.25 (s, C-1'), 146.48 (s, C-8a), 159.19 (s, C=O), 167.06 (s, C=O), 175.51 (s, C=S). *Anal.* Calcd for $C_{18}H_{21}N_3O_3S$: C, 60.14; H, 5.88; N, 11.69. Found: C, 60.01; H, 5.96; N, 11.67.

Methyl 1-benzyl-4-(3-ethoxycarbonylmethylureido)-1,2,5,6-tetrahydropyridine-3-carboxylate (3): The title compound was prepared in the same manner as **2a** from methyl 4-amino-1-benzyl-1,2,5,6-tetrahydropyridine-3-carboxylate **(1)** (0.98 g, 4 mmol) and ethyl isocyanatoacetate (0.52 g, 4 mmol), reaction time 5 h and recrystallized from ethanol as yellow needles. Yield: 0.94 g (63%); mp 104 ^{0}C. ^{1}H NMR ($CDCl_3$): δ_H 1.40 (t, *J* = 7.63 Hz, 3H, Me), 2.31 (t, *J* = 5.50 Hz, 2H, 5-H), 2.52 (t, *J* = 6.61 Hz, 2H, 6-H), 3.26 (s, 2H, 2-H), 3.56 (s, 2H, Ph-CH_2), 3.63 (s, 3H, Me), 4.37 (s, 2H, CH_2), 4.40 (q, *J* = 7.20 Hz, 2H, OCH_2), 7.25-7.40 (m, 5H, Ar-H), 8.36 (s, 1H, NH), 9.82 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ_C 14.01 (q, Me), 39.51 (t, C-5), 48.45 (t, CH_2), 49.77 (t, C-6), 50.62 (q, Me), 54.86 (t, C-2), 61.38 (t, Ph-CH_2), 61.60 (t, OCH_2), 101.87 (s, C-3), 127.65 (d, C-4'), 128.92 (d, C-3' and C-5'), 129.20 (d, C-2' and C-6'), 137.59 (s, C-1'), 145.47 (s, C-4), 157.29 (s, C=O), 167.07 (s, C=O), 169.15 (s, C=O). *Anal.* Calcd for $C_{19}H_{25}N_3O_5$: C, 60.78; H, 6.71; N, 11.19. Found: C, 60.66; H, 6.82; N, 11.08.

Ethyl 6-benzyl-1,2,3,4,5,6,7,8-octahydro-2,4-dioxopyrido[4,3-*d*]pyrimidine-3-acetate (2b): A solution of urea derivative **(3)** (0.75 g, 2 mmol) and sodium ethoxide (0.14 g, 2 mmol) in absolute ethanol (10 mL) was stirred for 1 h at rt. The solvent was removed *in vacuo* and the obtained solid was recrystallized from ethanol to give crystals **(2b)**. Yield: 0.50 g (74%); mp 210-211 ^{0}C. ^{1}H NMR (DMSO-d_6): δ_H 1.18 (t, *J* = 7.02 Hz, 3H, Me), 2.49 (t, *J* = 5.19 Hz, 2H, 8-H), 2.62 (t, *J* = 5.48 Hz, 2H, 7-H), 3.32 (s, 2H, 5-H), 3.61 (s, 2H, Ph-CH_2), 4.17 (q, *J* = 7.03 Hz, 2H, OCH_2), 5.10 (s, 2H, CH_2), 7.20-7.32 (m, 5H, Ar-H), 8.98 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ_C 13.91 (q, Me), 30.91 (t, C-8), 47.611 (t, C-7), 48.08 (t, C-5), 50.09 (t, CH_2), 61.22 (t, Ph-CH_2), 60.68 (t, OCH_2), 114.45 (s, C-4a), 127.21 (d, C-4'), 128.65 (d, C-3' and C-5'), 129.48 (d, C-2’ and C-6’), 139.85 (s, C-1’), 146.21 (s, C-8a), 153.91 (s, C=O), 166.29 (s, C=O), 169.08 (s, C=O). *Anal.* Calcd for $C_{18}H_{21}N_3O_4$: C, 62.95; H, 6.16; N, 12.23. Found: C, 62.06; H, 6.23; N, 12.16.

Ethyl 6-benzyl-3,4,5,6,7,8-hexahydro-2-methylthio-4-oxopyrido[4,3-*d*]pyrimidine-3-acetate (4): Method-A: To a solution of sodium methoxide (0.53 g, 10 mmol) in dry methanol (75 mL) was added thioxo compound **(2a)** (3.59 g, 10 mmol) and the mixture was stirred as the temperature raised to 60 ^{0}C. Methyl iodide (1.42 g, 10 mmol) was added while the mixture was refluxed under nitrogen for 2 h and then the mixture was cooled to give a solid. The solid was collected and recrystallized from ethanol. Yield: 2.57 g (69%).

Method B: A solution of methyl 4-amino-1-benzyl-1,2,5,6-tetrahydropyridine-3-carboxylate **(1)** (0.98 g, 4 mmol) and ethyl *N*-[bis(methylthio)methylene]glycinate (0.82 g, 4 mmol) in 8 mL of dry acetic acid was heated under reflux for 8 h. The solution was poured into an ice - water. The mixture was stirred for 1 h. The precipitated was collected by filtration and recrystallized from ethanol. Yield 0.86 g (58%). The compound is identical with the compound obtained by method A. mp 145-146 ^{0}C. ^{1}H NMR ($CDCl_3$): δ_H 1.15 (t, J = 7.10 Hz, 3H, Me), 2.49 (t, J = 5.19 Hz, 2H, 8-H), 2.60 (s, 3H, SMe), 2.64 (t, J = 5.49 Hz, 2H, 7-H), 3.30 (s, 2H, 5-H), 3.60 (s, 2H, Ph-CH_2), 4.25 (q, J = 7.00 Hz, 2H, OCH_2), 4.85 (s, 2H, CH_2), 7.22-7.40 (m, 5H, Ar-H). ^{13}C NMR ($CDCl_3$): δ_C 14.03 (q, SMe), 14.86 (q, Me), 27.26 (t, C-8), 47.06 (t, C-7), 47.60 (t, C-5), 44.20 (t, CH_2), 60.75 (t, Ph-CH_2), 61.73 (t, OCH_2), 111.26 (s, C-4a), 127.49 (d, C-4’), 128.36 (d, C-3’ and C-5’), 129.13 (d, C-2’ and C-6’), 134.89 (s, C-1’), 144.21 (s, C-8a), 157.80 (s, C-2), 162.20 (s, C=O), 166.88 (s, C=O). *Anal.* Calcd for $C_{19}H_{23}N_3O_3S$: C, 61.10; H, 6.20; N, 11.25. Found: C, 61.01; H, 6.26; N, 11.18.

Ethyl 6-benzyl-3,4,5,6,7,8-hexahydro-2-(1-pyrrolidinyl)-4-oxopyrido[4,3-*d*]pyrimidine-3-acetate (6a): A suspension of the thioxo product **(2a)** (5.74 g, 16 mmol) in phosphoryl chloride (100 mL, 1080 mmol) was refluxed at 120 ^{0}C for 22 h. Excess phosphoryl chloride was distilled off under vacuum. Ether (100 mL) was added and the mixture was stirred for 2 h. The solid was collected by filtration and washed with ether to afford chloro product **(5)**, mp 102 ^{0}C (air sensitive).

A solution of the crude chloro product **(5)** (0.36 g) and pyrrolidine (0.49 g, 1.5 mmol) in triethylamine (5 mL) was refluxed for 4 h. The solvent was evaporated *in vacuo*. The obtained solid was recrystallized from ethanol and ethyl acetate (3:1) to give **6a** as white crystals. Yield: 0.24 g (62%), mp 160-161 ^{0}C. ^{1}H NMR ($CDCl_3$): δ_H 1.27 (t, J = 7.10 Hz, 3H, Me), 1.70-1.90 (m, 4H, -CH_2-CH_2-), 2.54 (t, J = 5.20 Hz, 2H, 8-H), 2.78 (t, *J* = 5.50 Hz, 2H, 7-H), 3.35 (s, 2H, 5-H), 3.30-3.50 (m, 4H, H_2C-N-CH_2), 3.61 (s, 2H, Ph-CH_2), 4.30 (q, *J* = 7.00 Hz, 2H, CH_2O), 4.70 (s, 2H, CH_2), 7.25-7.40 (m, 5H, Ar-H). ^{13}C NMR (DMSO-d_6): δ_C 14.20 (q, Me), 25.40 (t, CH_2-CH_2), 26.54 (t, C-8), 46.09 (t, C-7), 47.20 (t, CH_2), 47.77 (t, C-5), 50.50 (t, H_2C-N-CH_2), 61.62 (t, Ph-CH_2), 61.88 (t, OCH_2), 111.04 (s, C-4a), 127.56 (d, C-4'), 128.71 (d, C-3' and C-5'), 129.64 (d, C-2' and C-6'), 136.98 (s, C-1'), 150.78 (s, C-8a), 159.70 (s, C-2), 162.13 (s, C=O), 167.32 (s, C=O). *Anal.* Calcd for $C_{22}H_{28}N_4O_3$: C, 66.64; H, 7.11; N, 14.13. Found: C, 66.69; H, 7.22; N, 14.19.

Ethyl 6-benzyl-3,4,5,6,7,8-hexahydro-2-(4-morpholinyl)-4-oxopyrido[4,3-*d*]pyrimidine-3-acetate (6b): The chloro derivative **(5)** was prepared by the method described above. A solution of the crude chloro product **(5)** (0.36 g) and morpholine (0.13 g, 1.5 mmol) in triethylamine (5 mL) was refluxed for 2 h. The solvent was evaporated *in vacuo*. The obtained solid was recrystallized from a mixture of ethanol and ethyl acetate (3:1) to give **6b** as white crystals. Yield: 0.26 g (65%); mp 135 ^{0}C. ^{1}H NMR ($CDCl_3$): δ_H 1.25 (t, *J* = 7.10 Hz, 3H, Me), 2.50 (t, *J* = 5.15 Hz, 2H, 8-H), 2.67 (t, *J* = 5.50 Hz, 2H, 7-H), 3.10 (m, 4H, -H_2C-N-CH_2-), 3.25 (s, 2H, 5-H), 3.59 (s, 2H, Ph-CH_2), 3.80 (m, 4H, -H_2C-O-CH_2-), 4.25 (q, *J* = 7.10 Hz, 2H, CH_2O), 4.65 (s, 2H, CH_2), 7.20-7.40 (m, 5H, Ar-H). ^{13}C NMR (DMSO-d_6): δ_C 13.97 (q, Me), 26.50 (t, C-8), 47.10 (t, C-7), 45.45 (t, CH_2), 47.60 (t, C-5), 50.47 (t, -H_2C-N-CH_2-), 61.50 (t, Ph-CH_2), 61.60 (t, OCH_2), 66.14 (t, -H_2C-O-CH_2-), 110.87 (s, C-4a), 137.25 (s, C-1'), 127.37 (d, C-4'), 128.92 (d, C-3' and C-5'), 129.69 (d, C-2' and C-6'), 150.56 (s, C-8a), 159.12 (s, C-2), 162.01 (s, C=O), 167.07 (s, C=O). *Anal.* Calcd for $C_{22}H_{28}N_4O_4$: C, 64.06; H, 6.84; N, 13.58. Found: C, 64.17; H, 6.95; N, 13.48.

1-Amino-7-benzyl-1,2,3,5,6,7,8,9-octahydroimidazo[1,2-*a*]pyrido[4,3-*d*]pyrimidine-2,5-dione (7): Method A: A solution of the crude chloro product **(5)** (0.72 g) and 99% of hydrazine hydrate (0.10 g, 3 mmol) in triethylamine (5 mL) was refluxed for 5 h. The solvent was evaporated *in vacuo*. The obtained solid was recrystallized from a mixture of ethanol and ethyl acetate (3:1) to give **7** as white crystals. Yield: 0.44 g (70%).

Method B: A solution of the methylthio derivative **(4)** (0.74g, 2 mmol) and 99% of hydrazine hydrate (5 mL, 102.87 mmol) in 8 mL of ethanol was heated under reflux for 8 h with stirring. The solvent was evaporated under reduced pressure. The solid was washed with water and recrystallized from isopropanol to give white crystals. Yield: 0.68 g (61%); mp 268 ^{0}C. ^{1}H NMR ($CDCl_3$): δ_H 2.48 (t, *J* = 4.88 Hz, 2H, 9-H), 2.62 (t, *J* = 5.49 Hz, 2H, 8-H), 3.30 (s, 2H, 6-H), 3.65 (s, 2H, Ph-CH_2), 4.40 (s, 2H, 3-H), 5.25 (s, 2H, NH_2), 7.20-7.40 (m, 5H, Ar-H). ^{13}C NMR (DMSO-d_6): δ_C 26.47 (t, C-9), 49.82 (t, C-3), 47.24 (t, C-8), 47.30 (t, C-6), 60.20 (t, Ph-CH_2), 111.09 (s, C-5a), 127.55 (d, C-4’), 128.45 (d, C-3’ and C-5’), 129.56 (d, C-2’ and C-6’), 136.67 (s, C-1’), 150.80 (s, C-9a), 154.75 (s, C-10a), 162.84 (s, C=O), 166.08 (s, C=O). *Anal.* Calcd for $C_{16}H_{17}N_5O_2$: C, 61.72; H, 5.50; N, 22.49. Found: C, 61.83; H, 5.56; N, 22.61.

7-Benzyl-2,3,6,7,8,9-hexahydro-5*H*-thiazolo[3,2-*a*]pyrido[4,3-*d*]pyrimidin-5-one (8): A solution of methyl 4-amino-1-benzyl-1,2,5,6-tetrahydropyridine-3-carboxylate **(1)** (0.98 g, 4 mmol) and 2-methylthio-2-thiazoline (0.66 g, 5 mmol) in dry acetic acid (6 mL) was heated to 100 ^{0}C for 5 h. After cooling to rt, crushed ice (100 g) was added and the mixture was stirred for 1 h. The separated product was collected and recrystallized from ethyl acetate to give **8** as red crystals. Yield: 0.71 g (60%); mp 98-99 ^{0}C. ^{1}H NMR ($CDCl_3$): δ_H 2.51 (t, J = 5.00 Hz, 2H, 9-H), 2.64 (t, J = 5.50 Hz, 2H, 8-H), 3.30 (s, 2H, 6-H), 3.58 (t, J = 7.50 Hz, 2H, 2-H), 3.68 (s, 2H, Ph-CH_2), 4.33 (t, J = 7.50 Hz, 2H, 3-H), 7.20-7.35 (m, 5H, Ar-H). ^{13}C NMR ($CDCl_3$): δ_C 26.82 (t, C-9), 28.46 (s, C-2), 44.10 (t, C-8), 45.93 (t, C-6), 49.52 (t, C-3), 60.94 (t, Ph-CH_2), 99.51 (s, C-5a), 127.41 (d, C-4’), 128.45 (d, C-3’ and C-5’), 129.17 (d, C-2’ and C-6’), 136.41 (s, C-1’), 148.35 (s, C-9a), 156.97 (s, C-10a), 162.89 (s, C=O). *Anal.* Calcd for $C_{16}H_{17}N_3OS$: C, 64.18; H, 5.72; N, 14.03. Found: C, 64.24; H, 5.79; N, 14.05.

8-Benzyl-3,4,7,8,9,10-hexahydro-2*H*,6*H*-pyrido[4',3':4,5]pyrimido[2,1-*b*][1,3]thiazin-6-one (9): The title compound was prepared in the same manner as **8** from methyl 4-amino-1-benzyl-1,2,5,6-tetrahydropyridine-3-carboxylate **(1)** (0.98 g, 4 mmol) and 5,6-dihydro-2-methylthio-4*H*-1,3-thiazine (0.73 g, 5 mmol). An analytical sample was recrystallized from a mixture of ethyl acetate and ether (3:1) to afford **9** as red crystals. Yield: 0.58 g (47%); mp 73-74 ^{0}C. ^{1}H NMR ($CDCl_3$): δ_H 2.50 (t, 2H, J = 4.90 Hz, 10-H), 2.30 (m, 2H, 3-H), 2.58 (t, J = 5.50 Hz, 2H, 9-H), 3.20 (t, J = 7.50 Hz, 2H, 2-H), 3.28 (s, 2H, 7-H), 3.60 (s, 2H, Ph-CH_2), 4.20 (t, 2H, J = 6.50 Hz, 4-H), 7.28-7.35 (m, 5H, Ar-H). ^{13}C NMR ($CDCl_3$): δ_C 22.93 (t, C-3), 26.64 (t, C-10), 27.72 (s, C-2), 46.01 (t, C-9), 40.88 (t, C-4), 46.92 (t, C-7), 60.42 (t, Ph-CH_2), 99.69 (s, C-5a), 127.33 (d, C-4’), 128.43 (d, C-3’ and C-5’), 128.76 (d, C-2’ and C-6’), 136.02 (s, C-1’), 147.82 (s, C-10a), 153.65 (s, C-11a), 161.90 (s, C=O). *Anal.* Calcd for $C_{17}H_{19}N_3OS$: C, 65.14; H, 6.11; N, 13.40. Found: C, 65.24; H, 6.03; N, 13.48.

General Procedure for the Cyclization Reaction: Synthesis of Compounds (10-13). A solution of methyl 4-amino-1-benzyl-1,2,5,6-tetrahydropyridine-3-carboxylate **(1)** (0.98 g, 4 mmol) and appropriate reagent (6 mmol) in hexamethylphosphoric triamide (HMPA, 5 mL) was heated to 160 ^{0}C for an appropriate period of time. After cooling to rt, crushed ice (70 g) was added and the mixture was stirred for 1 h. The resulting crystals were collected by filtration and were purified by recrystallization from an appropriate solvent.

7-Benzyl-2,3,6,7,8,9-hexahydro-1*H*,5*H*-imidazo[1,2-*a*]pyrido[4,3-*d*]pyrimidin-5-one (10): This compound was obtained from 2-methylthio-2-imidazoline, reaction time 5 h and recrystallized from methanol to give **10** as yellow crystals. Yield: 62%; mp 230-231 ^{0}C. ^{1}H NMR (CDCl$_3$): δ_H 2.42 (t, J = 4.88 Hz, 2H, 9-H), 2.71 (t, J = 5.49 Hz, 2H, 8-H), 3.25 (s, 2H, 6-H), 3.30 (t, J = 6.70 Hz, 2H, 2-H), 3.60 (s, 2H, Ph-CH$_2$), 4.70 (t, J = 6.70 Hz, 2H, 3-H), 7.23-7.32 (m, 5H, Ar-H), 8.14 (s, 1H, NH). ^{13}C NMR (CDCl$_3$): δ_C 26.80 (t, C-9), 47.25 (t, C-8), 43.34 (t, C-2), 44.80 (t, C-3), 47.44 (t, C-6), 60.49 (t, Ph-CH$_2$), 111.10 (s, C-5a), 127.40 (d, C-4'), 128.43 (d, C-3' and C-5'), 128.69 (d, C-2' and C-6'), 134.21 (s, C-1'), 150.91 (s, C-9a), 155.30 (s, C-10a), 166.04 (s, C=O). *Anal.* Calcd for $C_{16}H_{18}N_4O$: C, 68.06; H, 6.42; N, 19.84. Found: 67.92; C, H, 6.21; N, 19.97.

8-Benzyl-1,2,3,4,7,8,9,10-octahydro-6*H*-pyrido[4,3-*d*]pyrimido[1,2-*a*]pyrimidin-6-one (11): This compound was obtained from 2-methylthio-1,4,5,6-tetrahydropyrimidine, reaction time 3 h and recrystallized from methanol to give **11** as yellow crystals. Yield: 68%; mp 168-169 ^{0}C. ^{1}H NMR (CDCl$_3$): δ_H 1.90 (m, 2H, 3-H), 2.49 (t, J = 4.88 Hz, 2H, 10-H), 2.60 (t, J = 5.49 Hz, 2H, 9-H), 3.20 (t, J = 5.19 Hz, 2H, 2-H), 3.30 (s, 2H, 7-H), 3.60 (s, 2H, Ph-CH$_2$), 3.91 (t, J = 5.49 Hz, 2H, 4-H), 7.21-7.29 (m, 5H, Ar-H), 8.10 (s, 1H, NH). ^{13}C NMR (CDCl$_3$): δ_C 21.01 (s, C-3), 26.71 (t, C-10), 37.89 (s, C-2), 38.35 (s, C-4), 47.20 (t, C-9), 47.52 (t, C-7), 61.71 (t, Ph-CH$_2$), 105.54 (s, C-6a), 127.68 (d, C-4'), 128.32 (d, C-3' and C-5'), 128.83 (d, C-2' and C-6'), 136.57 (s, C-1'), 150.25 (s, C-10a), 157.08 (s, C-11a), 165.58 (s, C=O). *Anal.* Calcd for $C_{17}H_{20}N_4O$: C, 68.89; H, 6.80; N, 18.90 Found: C, 68.97; H, 6.84; N, 19.03.

8-Benzyl-7,8,9,10-tetrahydro-6*H*-pyrido[4,3-*d*]pyrimido[1,2-*a*]pyrimidin-6-one (12): This compound was obtained from 2-chloropyrimidine, reaction time 8 h and recrystallized from methanol to give **12** as yellow crystals. Yield: 48%; mp 280-281 ^{0}C. ^{1}H NMR (CDCl$_3$): δ_H 2.50 (t, J = 4.88 Hz, 2H, 10-H), 2.62 (t, J = 5.50 Hz, 2H, 9-H), 3.24 (s, 2H, 7-H), 3.60 (s, 2H, Ph-CH$_2$), 7.21-7.30 (m, 5H, Ar-H), 8.29-8.42 (m, 3H, 2-H, 3-H and 4-H). ^{13}C NMR (CDCl$_3$): δ_C 29.62 (t, C-10), 48.89 (t, C-9), 50.35 (t, C-7), 61.26 (t, Ph-CH$_2$), 109.26 (s, C-6a), 127.70 (d, C-4'), 128.33 (d, C-3' and C-5'), 129.05 (d, C-2' and C-6'), 132.7 7 (s, C-3), 136.90 (s, C-1'), 138.27 (s, C-2), 142.10 (s, C-4), 157.66 (s, C-10a), 158.02 (s, C-11a), 162.14 (s, C=O). *Anal.* Calcd for $C_{17}H_{16}N_4O$: C, 69.84; H, 5.51; N, 19.16. Found: C, 69.96; H, 5.63; N, 19.07.

2-Benzyl-1,2,3,4-tetrahydro-11*H*-pyrazino[1,2-*a*]pyrido[4,3-*d*]pyrimidin-11-one (13): This compound was obtained from 2-methylthio-2-pyrazine, reaction time 11 h and recrystallized from methanol to give **13** as colourless crystals. Yield: 32%; mp >300 ^{0}C. ^{1}H NMR ($CDCl_3$): δ_H 2.54 (t, J = 4.54 Hz, 2H, 4-H), 2.60 (t, 2H, J = 5.61 Hz, 3-H), 3.43 (s, 2H, 1-H), 3.62 (s, 2H, Ph-CH_2), 7.24-7.30 (m, 5H, Ar-H), 8.32 (d, J = 1.95 Hz, 1H, 8-H), 8.57 (d, J = 1.95 Hz, 1H, 9-H), 9.05 (s, 1H, 6-H). ^{13}C NMR ($CDCl_3$): δ_C 27.94 (t, C-4), 49.85 (t, C-3), 50.06 (t, C-1), 60.32 (t, Ph-CH_2), 124.80 (s, C-6a), 127.68 (d, C-4'), 128.13 (d, C-3' and C-5'), 128.74 (d, C-2' and C-6'), 136.80 (s, C-1'), 145.70 (s, C-8), 148.20 (s, C-9), 149.10 (s, C-6), 1565.24 (s, C-4a), 159.20 (s, C-5a), 162.90 (s, C=O). *Anal.* Calcd for $C_{17}H_{16}N_4O$: C, 69.84; H, 5.51; N, 19.16. Found: C, 69.70; H, 5.66; N, 19.24.

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