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ONE POT SYNTHESIS OF FUSED PYRIMIDINES FROM 2-[*N*-(METHYLTHIOTHIOCARBONYL)AMINO]ACETATE

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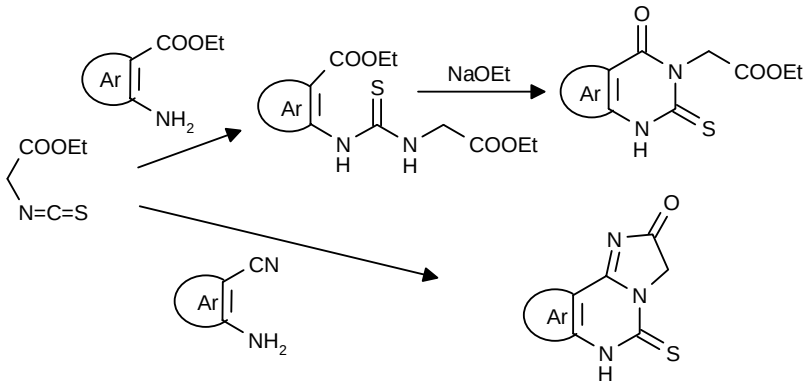
Abstract - A variety of 3-substituted fused pyrimidines **(4a-k)** are readily obtained from the 2-amino esters **(2a-k)** with 2-[*N*-(methylthiothiocarbonyl)-amino]acetate **(1)**. Condensed imidazo[1,2-*c*]pyrimidine ring system was also constructed in a one-pot process by reacting heteroaromatic 2-amino nitriles **(3a-l)** with **1**, obtaining a number of novel tri- and tetracyclic compounds **(5a-l)** .

Fused pyrimidines are found in a wide variety of natural products [e.g. purines, pyrrolopyrimidines, pyridopyrimidines, pteridines], pharmaceuticals, agrochemicals and veterinary products.[1-7] In recent papers,[8-11] we reported the reaction of heteroaromatic 2-amino esters or 2-amino nitriles with ethyl isothiocyanatoacetate giving fused pyrimidines or imidazopyrimidines, respectively (Scheme 1).



Scheme 1

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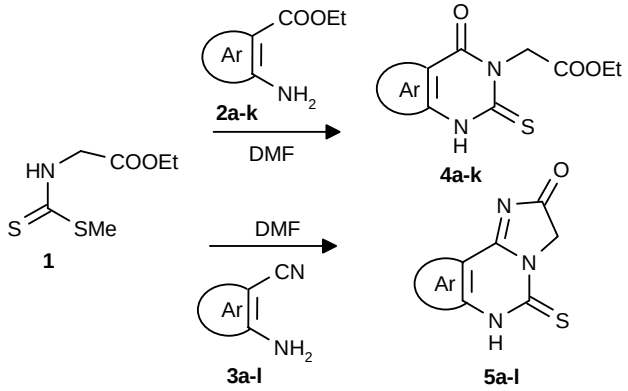
As illustrated in Scheme 2, the present work is aiming at the synthesis of similar products, using ethyl 2-[*N*-[(methylthiothiocarbonyl)amino]acetate **(1)** in DMF.



Scheme 2

Utilization of **1** seems promising, since the corresponding isocyanatoacetate as well as 2-chloroethyl isocyanate have already been used for cyclizing anthranilonitrile **(3a)** in a 2- or 3-step procedure, respectively.[12,13]

Here, we report a simple, one-pot reaction for the synthesis of 3-substituted pyrimidines and tri- or tetracyclic imidazopyrimidine systems by the reaction of 2-amino esters or 2-amino nitriles with ethyl 2-[*N*-[(methylthiothiocarbonyl)amino]acetate **(1)** in DMF.

The reaction of various 2-amino esters **(2a-k)** with **1** afforded cyclization products **(4a-k)** (Figure 1) by one-pot reactions in 40-55% yields presumably *via* an intermediate **G**.

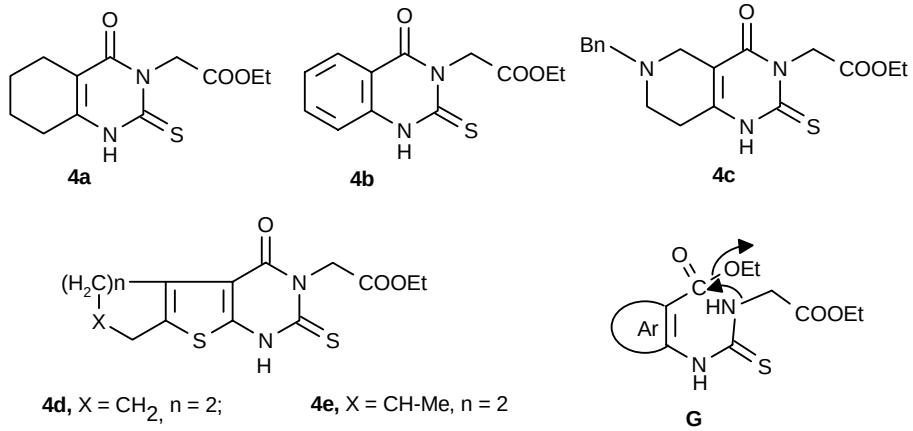


Figure 1

The conformity of the structure **(4a-k)** was proved by several evidences: comparison of chemical shifts between 2-(3,4-dihydro-2-methyl-4-oxoquinazolin-3-yl)acetic acid (from a ^{13}C NMR spectral data bank[14]) and methylthio derivatives[15,16] of **4b**. Moreover, the NMR values of **4b** is also good agreements with the literature values.[16]

The reaction of 2-amino nitriles **(3a-l)** with **1** gave the fused pyrimidines **(5a-l)** (Figure 2) by the one-pot reactions in 36-46% yields presumably *via* a thiourea intermediate **(5I)**, wherein imidazolidinyl derivative **(5L)** and diazepino derivative **(5M)** were ruled out by NMR spectroscopy. This method is useful for giving smooth access to tricyclic and tetracyclic hetero systems **(5a-l)**.

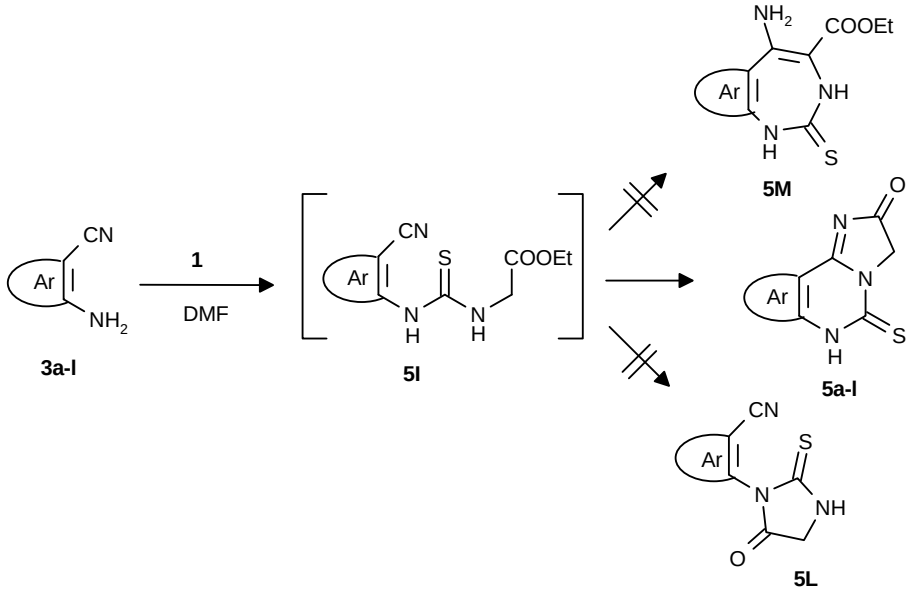


Figure 2

Thus, a series of imidazo[1,2-*c*]quinazoline **(5a)**, imidazo[1,2-*c*]thiazolo[5,4-*e*]pyrimidine **(5b)**, (benzo)furo[3,2-*e*]imidazo[1,2-*c*]pyrimidine **(5c,5d),** benzothieno[3,2-*e*]imidazo[1,2-*c*]pyrimidine **(5e,5f)**, imidazo[1,2-*c*]pyrido[4',3':4,5]thieno[3,2-*e*]pyrimidine **(3g,3h)**, imidazo[1,2-*c*](thio)pyrano[4',3':4,5]-thieno[3,2-*e*]pyrimidine **(5i,5j)**, and cyclo(hepta or penta)[4,5]thieno[3,2-*e*]imidazo[1,2-*c*]pyrimidine **(5k,5l)** were easily accessible from 2-amino nitriles **(3a-l)** and ethyl 2-[*N*-(methylthiothiocarbonyl)-amino]acetate **(1)** in DMF by a one-step reaction (Figure 3).

Annelation to such type of angular tri- and tetracyclic compounds **(5a-l)** was also established by Sauter[15,17] and Chowdhury[9,10,18] from 2-amino nitriles with *N*-[bis(methylthio)methylene]amino **(**BMMA) reagents. The structural assignment of compounds **(5a-l)** was based on the NMR spectral and elemental analytical data. Displacement reactions have been employed to create the middle ring of tricyclic or tetracyclic systems in one-step as described above. So, the concept of creating our desired tricyclic and

tetracyclic condensed systems in one-step *via* a double displacement process using **1** is demonstrated smoothly.

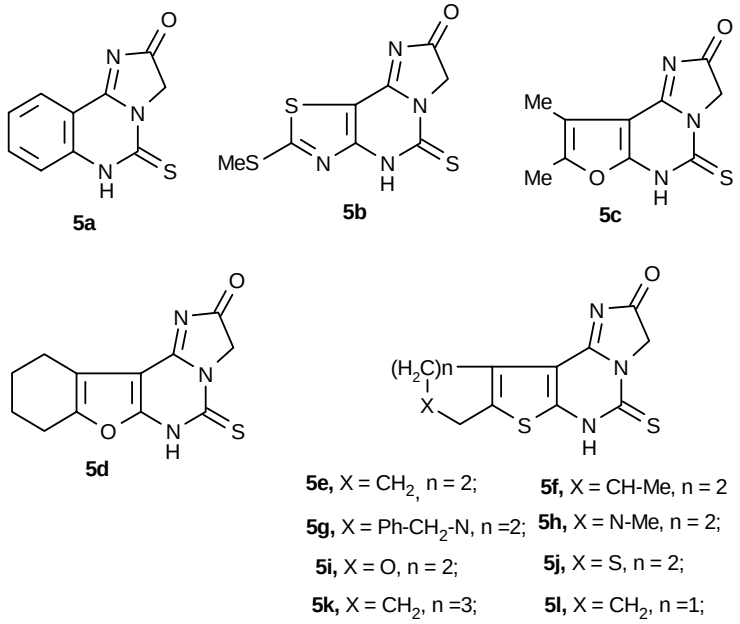


Figure 3

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 (internal standard TMS, solvents $CDCl_3$ or DMSO-d_6 respectively, δ-values in ppm) at the National Institute for Environmental Studies, Tsukuba, Japan. Elemental analyses were performed on an EA 1108 (Fisons Instruments) Elemental Analyzer.

Ethyl 2-[*N*-(methylthiothiocarbonyl)amino]acetate **(1)** was prepared from ethyl glycinate using the method reported.[10,15] Ethyl 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate **(2d)** and -3-carbonitrile **(3e)**, ethyl 2-amino-4,5,6,7-tetrahydro-6-methylbenzo[*b*]thiophene-3-carboxylate **(2e)** and -3-carbonitrile **(3f)**, ethyl 2-amino-6-benzyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxylate **(2f)** and -3-carbonitrile **(3g)**, ethyl 2-amino-4,5,6,7-tetrahydro-6-methylthieno[2,3-*c*]pyridine-3-carboxylate **(2g)** and -3-carbonitrile **(3h)**, ethyl 2-amino-4,7-dihydro-5*H*-thieno[2,3-*c*]pyran-3-carboxylate **(2h)** and -3-carbonitrile **(3i)**, ethyl 2-amino-4,7-dihydro-5*H*-thieno[2,3-*c*]thiopyran-3-carboxylate **(2i)** -3-carbonitrile **(3j)**, ethyl 2-amino-5,6,7,8-tetrahydro-4*H*-cyclohepta[b]thiophene-3-carboxylate **(2j)** and -3-carbonitrile **(3k)**, and ethyl 2-amino-5,6-dihydro-4*H*-cyclopenta[b]thiophene-3-carboxylate (**2k)** and -3-carbonitrile **(3j)** were obtained according to the literature procedures,[19-21] respectively. 4-Amino-2-methylthiothiazole-5-carbonitrile **(3b)**,[22] 2-amino-4,5-dimethylfuran-3-carbonitrile **(3c)**[23] and 2-amino-

4,5,6,7-tetrahydrobenzofuran-3-carbonitrile **(3d)**[10] were prepared according to the procedures in the literatures. Anthranilonitrile **(3a)**, ethyl anthranilate **(2b)**, methyl 2-amino-1-cyclohexene-1-carboxylate **(2a)** and methyl 4-amino-1-benzyl-1,2,5,6-tetrahydropyridine-3-carboxylate **(2c)** were purchased from Kanto Chemicals.

General Procedure for Cyclization Reactions: Synthesis of Compounds (4a-k and 5a-l). A solution of appropriate 2-amino ester or 2-amino nitrile (10 mmol) and 2-[*N*-(methylthiothiocarbonyl)-amino]acetate **(1)** (10 mmol) in 6 mL of DMF was refluxed for 8-10 h. The reaction mixture was cooled and poured onto the crushed ice. The resulting solids were collected by filtration and recrystallized from an appropriate solvent.

Ethyl 2-(1,2,3,4,5,6,7,8-octahydro-4-oxo-2-thioxoquinazolin-3-yl)acetate (4a): Prepared from **2a** as white crystals (ethanol), yield 52%, mp 187-189 ^{0}C. ^{1}H NMR ($CDCl_3$): δ 1.21 (t, *J* = 7.1 Hz, 3H, Me), 1.70 (m, 4H, 6-H and 7-H), 2.30 (t, *J* = 7.6 Hz, 4H, 5-H and 8-H), 4.18 (q, *J* = 7.1 Hz, 2H, OCH_2), 4.59 (s, 2H, CH_2), 10.35 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 13.96 (q, Me), 20.98 (t, C-6), 21.04 (t, C-7), 21.45 (t, C-5), 26.07 (t, C-8), 41.25 (t, CH_2), 61.51 (t, OCH_2), 109.76 (s, C-4a), 147.52 (s, C-8a), 154.55 (s, C=O), 167.23 (s, C=O), 170.79 (s, C=S). *Anal.* Calcd for $C_{12}H_{16}N_2O_3S$: C, 53.72; H, 6.01; N, 10.44. Found: C, 53.81; H, 5.94; N, 10.35.

Ethyl 2-(1,2,3,4-tetrahydro-4-oxo-2-thioxoquinazolin-3-yl)acetate (4b): Prepared from **2b** as colorless crystals (ethanol), yield 47%, mp 223-225 ^{0}C. ^{1}H NMR ($CDCl_3$): δ 1.28 (t, *J* = 7.1 Hz, 3H, Me), 4.25 (q, *J* = 7.1 Hz, 2H, OCH_2), 5.15 (s, 2H, CH_2), 8.20 (m, 1H, 8-H), 7.30-7.85 (m, 3H, 5-H, 6-H and 7-H), 8.20 (m, 1H, 8-H), 10.30 (s, 1H, NH). ^{13}C NMR ($CDCl_3$ $CDCl_3$): δ 14.52 (q, Me), 45.32 (t, CH_2), 61.64 (t, OCH_2), 118.68 (s, C-4a), 125.55 (d, C-6), 125.98 (d, C-7), 126.81 (d, C-5), 134.45 (d, C-8), 147.85 (s, C-8a), 156.24 (s, C=O), 167.25 (s, C=O), 173.13 (s, C=S). *Anal.* Calcd for $C_{12}H_{12}N_2O_3S$: C, 54.53; H, 4.57; N, 10.59. Found: C, 54.38; H, 4.61; N, 10.47.

Ethyl 2-(6-benzyl-1,2,3,4,5,6,7,8-octahydro-4-oxo-2-thioxopyrido[4,3-*d*]pyrimidin-3-yl)acetate (4c): Prepared from **2c** as brown crystals (ethanol), yield 45%, mp 188-190 ^{0}C. ^{1}H NMR ($CDCl_3$): δ 1.20 (t, *J* = 7.1 Hz, 3H, Me), 2.46 (t, *J* = 5.2 Hz, 2H, 8-H), 2.60 (t, *J* = 5.5 Hz, 2H, 7-H), 3.28 (s, 2H, 5-H), 3.60 (s, 2H, Ph-CH_2), 4.15 (q, *J* = 7.1 Hz, 2H, OCH_2), 5.11 (s, 2H, CH_2), 7.20-7.38 (m, 5H, Ar-H), 11.05 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 14.05 (q, Me), 26.45 (t, C-8), 47.08 (t, C-7), 47.78 (t, C-5), 48.51 (t, CH_2), 61.65 (t, Ph-CH_2), 61.88 (t, OCH_2), 110.85 (s, C-4a), 127.24 (d, C-4'), 128.95 (d, C-3' and C-5'), 129.69

(d, C-2' and C-6'), 137.25 (s, C-1'), 146.50 (s, C-8a), 159.23 (s, C=O), 167.12 (s, C=O), 175.50 (s, C=S). *Anal.* Calcd for $C_{18}H_{21}N_3O_3S$: C, 60.14; H, 5.88; N, 11.69. Found: C, 59.99; H, 5.94; N, 11.75.

Ethyl 2-(1,2,3,4,5,6,7,8-octahydro-4-oxo-2-thioxo[1]benzothieno[2,3-*d*]pyrimidin-3-yl)acetate (4d): Prepared from **2d** as yellow crystals (ethanol), yield 55%, mp 220-222 ^{0}C. ^{1}H NMR ($CDCl_3$): δ 1.31 (t, *J* = 7.1 Hz, 3H, Me), 1.85 (m, 4H, 6-H and 7-H), 2.65 (m, 2H, 5-H), 2.84 (m, 2H, 8-H), 4.24 (q, *J* = 7.1 Hz, 2H, OCH_2), 5.22 (s, 2H, CH_2), 11.35 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 13.75 (q, Me), 21.42 (t, C-6), 22.36 (t, C-7), 23.98 (t, C-5), 24.61 (t, C-8), 46.31 (t, CH_2), 60.72 (t, OCH_2), 115.37 (s, C-4b), 128.35 (s, C-4a), 131.12 (s, C-8a), 148.92 (s, C-9a), 156.41 (s, C=O), 167.12 (s, C=O), 173.60 (s, C=S). *Anal.* Calcd for $C_{14}H_{16}N_2O_3S_2$: C, 51.83; H, 4.97; N, 8.63. Found: C, 51.92; H, 4.99; N, 8.52.

Ethyl 2-(1,2,3,4,5,6,7,8-octahydro-7-methyl-4-oxo-2-thioxo[1]benzothieno[2,3-*d*]pyrimidin-3-yl)acetate (4e): Prepared from **2e** as white crystals (ethanol), yield 47%), mp 225-227 ^{0}C. ^{1}H NMR ($CDCl_3$): δ 1.05 (d, *J* = 6.4 Hz, 1H, 7-Me), 1.33 (t, *J* = 7.1 Hz, 3H, Me), 1.82-3.04 (m, 7H, 5-H, 6-H, 7-H and 8-H), 4.26 (q, *J* = 7.1 Hz, 2H, OCH_2), 5.23 (s, 2H, CH_2), 10.75 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 13.65 (q, Me), 20.80 (t, 7-Me), 24.21 (t, C-6), 28.65 (d, C-7), 29.51 (t, C-5), 31.85 (t, C-8), 46.22 (t, CH_2), 60.65 (t, OCH_2), 115.16 (s, C-4b), 127.88 (s, C-4a), 130.71 (s, C-8a), 148.95 (s, C-9a), 156.09 (s, C=O), 166.92 (s, C=O), 173.55 (s, C=S). *Anal.* Calcd for $C_{15}H_{18}N_2O_3S_2$: C, 53.23; H, 5.36; N, 8.28. Found: C, 53.35; H, 5.28; N, 8.16.

Ethyl 2-(7-benzyl-1,2,3,4,5,6,7,8-octahydro-4-oxo-2-thioxopyrido[4',3':4,5]thieno[2,3-*d*]pyrimidin-3-yl)acetate (4f): Prepared from **2f** as red crystals (ethanol), yield 46%, mp 124-126 ^{0}C. ^{1}H NMR ($CDCl_3$): δ 1.15 (t, *J* = 7.1 Hz, 3H, Me), 2.90 (t, *J* = 5.2 Hz, 2H, 5-H), 3.33 (t, *J* = 5.5 Hz, 2H, 6-H), 3.76 (s, 2H, 8-H), 3.89 (s, 2H, CH_2-Ph), 4.20 (q, *J* = 7.1 Hz, 2H, OCH_2), 5.10 (s, 2H, CH_2), 7.29-7.54 (m, 5H, Ar-H). ^{13}C NMR (DMSO-d_6): δ 14.01 (q, Me), 24.54 (t, C-5), 46.58 (t, C-6), 48.61 (t, C-8), 50.17 (t, CH_2), 60.24 (t, CH_2-Ph), 60.65 (t, OCH_2), 114.64 (s, C-4b), 125.27 (s, C-1'), 127.40 (d, C-4'), 128.35 (d, C-2' and C-6'), 129.15 (d, C-3' and C-5') 129.27 (s, C-4a), 136.50 (s, C-8a), 150.67 (s, C-9a), 156.23 (s, C=O), 167.45 (s, C=O), 173.89 (s, C=S). *Anal.* Calcd for $C_{20}H_{21}N_3O_3S_2$: C, 57.81; H, 5.09; N, 10.11. Found: C, 57.65; H, 5.01; N, 9.85.

Ethyl 2-(1,2,3,4,5,6,7,8-octahydro-7-methyl-4-oxo-2-thioxopyrido[4',3':4,5]thieno[2,3-*d*]pyrimidin-3-yl)acetate (4g): Prepared from **2g** as brown crystals (ethanol), yield 40 %; mp 172-174 ^{0}C. ^{1}H NMR (DMSO-d_6): δ 1.22 (t, *J* = 7.1 Hz, 3H, Me), 2.60 (s, 3H, N-Me), 3.25 (m, 4H, 5-H and 6-H), 3.92 (s, 2H,

8-H), 4.10 (q, *J* = 7.1 Hz, 2H, OCH_2), 5.15 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6): δ 14.05 (q, Me), 23.65 (t, C-6), 42.91 (q, N-Me), 48.47 (t, C-5), 50.37 (t, C-8), 51.21 (t, CH_2), 60.65 (t, OCH_2), 113.48 (s, C-4b), 120.21 (s, C-4a), 128.01 (s, C-8a), 157.41 (s, C-9a), 157.98 (s, C=O), 167.64 (s, C=O), 175.19 (s, C=S). *Anal.* Calcd for $C_{20}H_{21}N_3O_3S_2$: C, 57.81; H, 5.09; N, 10.11. Found: C, 57.96; H, 5.15; N, 9.86.

Ethyl 2-(1,3,4,5,6,8-hexahydro-4-oxo-2-thioxo-2*H*-pyrano[4',3':4,5]thieno[2,3-*d*]pyrimidin-3-yl)acetate (4h): Prepared from **2h** as yellow crystals (ethanol), yield 45%, mp 226-227 ^{0}C. ^{1}H NMR (DMSO-d_6): δ 1.29 (t, *J* = 7.1 Hz, 3H, Me), 2.81 (t, *J* = 5.2 Hz, 2H, 5-H), 3.89 (t, *J* = 5.5 Hz, 2H, 6-H), 4.25 (q, *J* = 7.1 Hz, 2H, OCH_2), 4.65 (s, 2H, CH_2), 4.68 (s, 2H, 8-H), 8.67 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 14.18 (q, Me), 26.99 (t, C-5), 46.18 (t, CH_2), 60.99 (t, OCH_2), 64.67 (t, C-6), 64.94 (t, C-8), 112.45 (s, C-4b), 128.62 (s, C-4a), 136.56 (s, C-8a), 150.42 (s, C-9a), 156.45 (s, C=O), 166.84 (s, C=O), 170.77 (s, C=S). *Anal.* Calcd for $C_{13}H_{14}N_2O_4S_2$: C, 47.83; H, 4.32; N, 8.58. Found: C, 47.75; H, 4.40; N, 8.47.

Ethyl 2-(1,3,4,5,6,8-hexahydro-4-oxo-2-thioxo-2*H*-thiopyrano[4',3':4,5]thieno[2,3-*d*]pyrimidin-3-yl)acetate (4i): Prepared from **2i** as yellow needles (ethanol), yield 49%, mp 215-218 ^{0}C. ^{1}H NMR ($CDCl_3$): δ 1.26 (t, *J* = 7.1 Hz, 3H, Me), 2.84 (t, *J* = 6.1 Hz, 2H, 6-H), 2.99 (t, *J* = 5.6 Hz, 2H, 5-H), 4.25 (q, *J* = 7.1 Hz, 2H, OCH_2), 4.48 (s, 2H, CH_2), 3.70 (s, 2H, 8-H), 9.85 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6): δ 14.05 (q, Me), 25.09 (t, C-6), 25.86 (t, C-5), 26.90 (t, C-8), 46.15 (t, CH_2), 60.65 (t, OCH_2), 111.05 (s, C-4b), 125.29 (s, C-4a), 132.21 (s, C-8a), 140.14 (s, C-9a), 156.15 (s, C=O), 166.25 (s, C=O), 170.27 (s, C=S). *Anal.* Calcd for $C_{13}H_{14}N_2O_3S_3$: C, 45.59; H, 4.12; N, 8.18. Found: C, 45.71; H, 4.18; N, 8.25.

Ethyl 2-(1,3,4,5,6,7,8,9-octahydro-4-oxo-2-thioxo-2*H*-cyclohepta[4,5]thieno[2,3-*d*]pyrimidin-3-yl)-acetate (4j): Prepared from **2j** as white crystals (ethanol), yield 48%, mp 202-204 ^{0}C. ^{1}H NMR ($CDCl_3$): δ 1.25 (t, *J* = 7.1 Hz, 3H, Me), 1.68 (m, 4H, 6-H and 7-H), 1.95 (m, 2H, 8-H), 2.75 (m, 2H, 5-H), 3.21 (m, 2H, 9-H), 4.20 (q, *J* = 7.1 Hz, 2H, OCH_2), 5.20 (s, 2H, CH_2), 10.25 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 14.05 (q, Me), 26.75 (t, C-7), 27.08 (t, C-6), 27.45 (t, C-8), 29.35 (t, C-5), 32.14 (t, C-9), 47.15 (t, CH_2), 61.66 (t, OCH_2), 117.12 (s, C-4b), 132.97 (s, C-4a), 137.50 (s, C-9a), 146.76 (s, C-10a), 156.69 (s, C=O), 167.74 (s, C=O), 173.59 (s, C=S). *Anal.* Calcd for $C_{15}H_{18}N_2O_3S_2$: C, 53.23; H, 5.36; N, 8.28. Found: C, 53.11; H, 5.40; N, 8.12.

Ethyl 2-(1,3,4,5,6,7-hexahydro-4-oxo-2-thioxo-2*H*-cyclopenta[4,5]thieno[2,3-*d*]pyrimidin-3-yl)acetate (4k): Prepared from **2k** as yellow crystals (ethanol), yield 44%, mp 218-220 ^{0}C. ^{1}H NMR ($CDCl_3$): δ 1.25 (t, *J* = 7.1 Hz, 3H, Me), 2.43 (m, 2H, 6-H), 2.85 (m, 4H, 5-H and 7-H), 4.14 (q, *J* = 7.1 Hz, 2H,

OCH_2), 5.20 (s, 2H, CH_2), 10.21 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 13.74 (q, Me), 27.60 (t, C-6), 27.95 (t, C-5), 28.34 (t, C-7), 46.31 (t, CH_2), 60.68 (t, OCH_2), 112.45 (s, C-4b), 133.61 (s, C-4a), 140.15 (s, C-7a), 153.38 (s, C-8a), 155.94 (s, C=O), 166.87 (s, C=O), 173.81 (s, C=S). *Anal.* Calcd for $C_{14}H_{16}N_2O_3S_2$: C, 51.83; H, 4.97; N, 8.63. Found: C, 51.85; H, 4.92; N, 8.80.

5,6-Dihydro-5-thioxoimidazo[1,2-*c*]quinazolin-2(3*H*)-one (5a): Prepared from **3a** as brown crystals (ethanol), yield 41%, mp >320 ^{0}C. ^{1}H NMR (DMSO-d_6): δ 4.59 (s, 2H, 3-H), 7.55 (m, 2H, 8-H and 9-H), 7.76 (m, 1H, 10-H), 8.05 (m, 1H, 7-H), 10.65 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 53.45 (t, C-3), 110.81 (t, C-9), 116.05 (d, C-8), 125.11 (d, C-10), 127.35 (d, C-7), 136.94 (s, C-10a), 139.56 (s, C-7a), 168.02 (s, C-10b), 168.18 (s, C=S), 184.65 (s, C=O). *Anal.* Calcd for $C_{10}H_7N_3OS$: C, 55.29; H, 3.25; N, 19.34. Found: C, 55.19; H, 3.09; N, 19.08.

4,5-Dihydro-2-methylthio-5-thioxoimidazo[1,2-*c*]thiazolo[5,4-*e*]pyrimidin-8(7*H*)-one (5b): Prepared from **3b** as red crystals (ethanol), yield: 39%, mp >320 ^{0}C. ^{1}H NMR (DMSO-d_6): δ 4.42 (s, 2H, 7-H), 2.70 (s, 3H, Me), 10.20 (s, 1H, NH). *Anal.* Calcd. for $C_8H_6N_4OS_3$: C, 35.54; H, 2.24; N, 20.70. Found: C, 35.65; H, 2.45; N, 20.91.

5,6-Dihydro-8,9-dimethyl-5-thioxofuro[3,2-*e*]imidazo[1,2-*c*]pyrimidin-2(3*H*)-one (5c): Prepared from **3c** as red crystals (ethanol), yield 40%, mp 210-212 ^{0}C. ^{1}H NMR (DMSO-d_6): δ 2.16 (s, 3H, 9-Me), 2.28 (s, 3H, 8-Me), 4.35 (s, 2H, 3-H), 10.42 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 14.15 (q, 9-Me), 14.45 (q, 8-Me), 53.32 (t, C-3), 95.48 (s, C-9), 107.55 (s, C-9a), 124.28 (s, C-8), 148.65 (s, C-9b), 166.17 (s, C=S), 170.35 (s, C-6a), 172.85 (s, C=O). *Anal.* Calcd for $C_{10}H_9N_3O_2S$: C, 51.05; H, 3.85, N, 17.86. Found: C, 50.91; H, 3.93; N, 17.95.

5,6,8,9,10,11-Hexahydro-5-thioxobenzofuro[3,2-*e*]imidazo[1,2-*c*]pyrimidin-2(3*H*)-one (5d): Prepared from **3d** as red crystals (ethanol), yield 42 %, mp 276-278 ^{0}C. ^{1}H NMR (DMSO-d_6): δ 1.65-1.90 (m, 4H, 9-H and 10-H), 2.43-2.70 (m, 4H, 8-H and 11-H), 4.60 (s, 2H, 3-H). ^{13}C NMR (DMSO-d_6): δ 20.51 (t, C-10), 21.65 (t, C-11 and C-9), 22.18 (t, C-8), 53.49 (t, C-3), 94.26 (s, C-11a), 110.28 (s, C-11b), 149.65 (s, C-7a), 151.19 (s, C-11c), 166.48 (s, C=S), 170.01 (s, C-6a), 172.24 (s, C=O). *Anal.* Calcd for $C_{12}H_{11}N_3O_2S$: C, 55.16; H, 4.24; N, 16.08. Found: C, 55.30; H, 4.42; N, 16.19.

5,6,8,9,10,11-Hexahydro-5-thioxo[1]benzothieno[3,2-*e*]imidazo[1,2-*c*]pyrimidin-2(3*H*)-one (5e): Prepared from **3e** as brown crystals (ethanol-DMF), 46%, mp >320^{0}C. ^{1}H NMR (DMSO-d_6): δ 1.85 (m, 4H, 9-H and 10-H), 2.55-2.80 (m, 4H, 8-H and 11-H), 4.35 (s, 2H, 3-H). ^{13}C NMR (DMSO-d_6): δ 21.10 (t, C-10), 22.12 (t, C-9), 24.00 (t, C-11), 24.40 (t, C-8), 51.97 (t, C-3), 111.05 (s, C-11a), 129.52 (s, C-116), 130.35 (s, C-7a), 153.85 (s, C-6a), 162.41 (s, C-11c), 166.51 (s, C=S), 182.11 (s, C=O). *Anal.* Calcd for $C_{12}H_{11}N_3OS_2$: C, 51.96; H, 4.00; N, 15.15. Found: C, 52.21; H, 3.95; N, 14.91.

5,6,8,9,10,11-Hexahydro-9-Methyl-5-thioxo[1]benzothieno[3,2-*e*]imidazo[1,2-*c*]pyrimidin-2(3*H*)-one (5f): Prepared from **3f** as yellow crystals (ethanol), yield 39%, mp 299-301 ^{0}C. ^{1}H NMR (DMSO-d_6): δ 1.15 (d, J = 6.4 Hz, 3H, 9-Me), 1.82-2.95 (m, 7H, 8-H, 9-H, 10-H and 11-H), 4.45 (s, 2H, 3-H). *Anal.* Calcd for $C_{13}H_{13}N_3OS_2$: C, 55.59; H, 4.50; N, 14.42. Found: C, 55.71; H, 4.39; N, 14.56.

9-Benzyl-5,6,8,9,10,11-octahydro-2-oxo-5-thioxoimidazo[1,2-*c*]pyrido[4',3:4,5]thieno[3,2-*e*]pyrimidin-2(3*H*)-one (5g): Prepared from **3g** as red crystals (ethanol-chloroform), yield 44%, mp 250-252 ^{0}C. ^{1}H NMR ($CDCl_3$): δ 3.30-3.38 (m, 4H, 10-H and 11-H), 4.02 (s, 2H, 8-H), 4.13 (s, 2H, CH_2-Ph), 4.25 (s, 2H, 3-H), 7.30-7.55 (m, 5H, Ar-H). ^{13}C NMR (DMSO-d_6): δ 23.59 (t, C-11), 48.65 (t, C-10), 49.68 (t, C-8), 53.25 (t, C-3), 59.45 (t, CH_2-Ph), 109.31 (s, C-11a), 122.65 (s, C-1'), 126.92 (d, C-4'), 128.51 (d, C-2' and C-6'), 128.57 (d, C-3' and C-5') 130.12 (s, C-11b), 136.56 (s, C-8a), 133.16 (s, C-7a), 162.47 (s, C-6a), 163.38 (s, C-11c), 169.45 (s, C=S), 182.64 (s, C=O). *Anal.* Calcd for $C_{18}H_{16}N_4OS_2$: C, 58.67; H, 4.38; N, 15.20. Found: C, 58.45; H, 4.49; N, 15.03.

5,6,8,9,10,11-Hexahydro-9-methyl-5-thioxoimidazo[1,2-*c*]pyrido[4',3:4,5]thieno[3,2-*e*]pyrimidin-2(3*H*)-one (5h): Prepared from **3h** as red crystals (dimethyl sulfoxide), yield 36%, mp 270-272 ^{0}C. ^{1}H NMR ($CDCl_3$): δ 2.95 (s, 3H, N-Me), 3.12 (m, 2H, 11-H), 3.54 (m, 2H, 10-H). 4.15 (s, 2H, 8-H), 4.30 (s, 2H, 3-H). *Anal.* Calcd for $C_{12}H_{12}N_4OS_2$: C, 49.30; H, 4.14; N, 19.16. Found: C, 49.01; H, 4.32; N, 18.99.

6,8,10,11-Terahydro-5-thioxo-5*H*-imidazo[1,2-*c*]pyrano[4',3':4,5]thieno[3,2-*e*]pyrimidin-2(3*H*)-one (5i): Prepared from **3i** as red crystals (ethanol), yield 40%, mp 270 ^{0}C (decomp). ^{1}H NMR (DMSO-d_6): δ 2.82 (t, J = 4.8 Hz, 2H, 11-H), 3.95 (t, J = 5.1 Hz, 2H, 10-H), 4.40 (s, 2H, 3-H), 4.69 (s, 2H, 8-H). ^{13}C NMR (DMSO-d_6): δ_C 25.37 (t, C-11), 52.61 (t, C-3), 63.59 (t, C-10), 64.39 (t, C-8), 111.51 (s, C-11a), 126.91 (s, C-11b), 128.24 (s, C-7a), 159.14 (s, C-6a), 161.83 (s, C-11c), 167.48 (s, C=S), 181.55 (s, C=O). *Anal.* Calcd for $C_{11}H_9N_3O_2S_2$: C, 47.29; H, 3.24; N, 15.04. Found: C, 47.40; H, 3.31; N, 15.19.

6,8,10,11-Tetrahydro-5-thioxo-5*H*-imidazo[1,2-*c*]thiopyrano[4',3':4,5]thieno[3,2-*e*]pyrimidin-2(3*H*)-one (5j): Prepared from **3j** as red crystals (ethanol), yield 43%, mp >320 ^{0}C. ^{1}H NMR (DMSO-d_6): δ 2.80-3.15 (m, 4H, 10-H and 11-H), 3.90 (s, 2H, 8-H), 4.35 (s, 2H, 3-H). ^{13}C NMR (DMSO-d_6): δ 24.11 (t, C-10), 24.30 (t, C-11), 26.83 (t, C-8), 52.41 (t, C-3), 111.25 (s, C-11a), 126.88 (s, C-11b), 129.23 (s, C-7a), 161.51 (s, C-6a), 162.40 (s, C-11c), 166.86 (s, C=S), 182.49 (s, C=O). *Anal.* Calcd for $C_{11}H_9N_3OS_3$: C, 44.73; H, 3.07; N, 14.22. Found: C, 44.91; H, 3.18; N, 14.05.

6,8,9,10,11,12-Hexahydro-5-thioxo-5*H*-cyclohepta[4,5]thieno[3,2-*e*]imidazo[1,2-*c*]pyrimidin-2(3*H*)-one (5k): Prepared from **3e** as red crystals (ethanol-chloroform), yield 39%, mp >320 ^{0}C. ^{1}H NMR (DMSO-d_6): δ 1.50-1.90 (m, 6H, 9-H, 10-H and 11-H), 2.85 (m, 2H, 12-H), 3.32 (m, 2H, 8-H), 4.30 (s, 2H, 3-H). *Anal.* Calcd for $C_{13}H_{13}N_3OS_2$: C, 55.59; H, 4.50; N, 14.42. Found: C, 55.43; H, 4.36; N, 14.27.

6,8,9,10-Tetrahydro-5-thioxo-5*H*-cyclopenta[4,5]thieno[3,2-*e*]imidazo[1,2-*c*]pyrimidin-2(3*H*)-one (5l): Prepared from **3l** as red crystals (ethanol-chloroform), yield 38%, mp >320 ^{0}C. ^{1}H NMR (DMSO-d_6): δ 2.80-3.65 (m, 6H, 8-H, 9-H and 10-H), 4.55 (s, 2H, 3-H). *Anal.* Calcd for $C_{11}H_9N_3OS_2$: C, 50.17; H, 3.44; N, 15.96. Found: C, 50.35; H, 3.37; N, 15.85.

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REFERENCES

1. A. R. Katritzky and C. W. Rees, "Comprehensive Heterocyclic Chemistry", Vol. 1, Pergamon Press, 1984, pp. 143-221.
2. B. Roth and C. C. Cheng, "Progress in Medicinal Chemistry", Vol. 19, ed. by G. P. Ellis and G. B. West, Elsevier Biomedical Press, New York, 1982, p. 267.
3. L. F. Kuyper, J. M. Garvey, D. P. Baccanari, J. N. Champness, D. K. Stammers, and C. R. Beddell, *Bioorg. Med. Chem.*, 1996, **4**, 593.
4. M. Chebib, D. McKeveney, and R. J. Quinn, *Bioorg. Med. Chem.*, 2000, **8**, 2581.
5. A. Albert, "Advances in Heterocyclic Chemistry", Vol. 39, ed. by A. R. Katritzky, Academic Press, New York, NY, 1986, p. 117.
6. J. Chern, P. Tao, M. Yen, G. Lu, C. Shiau, Y. Lai, S. Chien, and C. Chan, *J. Med. Chem.*, 1993, **36**, 2196.

7. C. Petrie, B. H. Cottam, A. P. Mckernam, K. R. Robins, and R. G. Revankar, *J. Med. Chem.,* 1985, **28**, 1010.
8. A. Z. M. S. Chowdhury and Y. Shibata, *Heterocycles*, 2001, **55**, 115.
9. A. Z. M. S. Chowdhury and Y. Shibata, *Chem. Pharm. Bull.*, 2001, **49**, 391.
10. A. Z. M. S. Chowdhury, *J. Bangladesh Acad. Sci.,* 1999, **23**, 59.
11. F. Sauter, J. Fröhlich, A. Z. M. S. Chowdhury, and C. Hametner, *Acta Chim. Slov.*, 1996, **43**, 365.
12. E. P. Papadopoulos, *J. Heterocycl. Chem.,* 1980, **17**, 1553.
13. E. P. Papadopoulos, *J. Heterocycl. Chem.,* 1981, **18**, 515.
14. H. Kalchhauser and W. Robein, *J. Chem. Inform. Comput. Sci*., 1985, **25**, 103.
15. F. Sauter, J. Fröhlich, K. Blasl, and K. Gewald, *Heterocycles*, 1995, **40**, 851.
16. F. Kienzle, A. Kaiser, and E. Minder, *Helv. Chim. Acta,* 1983, **66**, 148.
17. F. Sauter, J. Fröhlich, and A. Z. M. S. Chowdhury, *Sci. Pharm.*, 1996, **64**, 647.
18. A. Z. M. S. Chowdhury, M. S. Rahman, M. M. H. Bhuiyan, and L. Yasmin, *Pakistan J. Sci. Ind. Res.*, 2000, **43**, 201.
19. K. Gewald, E. Schinke, and H. Bottcher, *Chem. Ber.,* 1966, **94**, 99.
20. E. F. Elslager, P. Jacob, and L. M. Werbel, *J. Heterocycl. Chem*., 1972, **9**, 775.
21. A. Rosowsky, M. Chaykovsky, K. K. N. Chen, M. Lin, and E. J. Modest, *J. Med. Chem*., 1973, **16**, 185.
22. D. Wobig, *Liebigs Ann. Chem.,* 1972, **764**, 125.
23. J. Prousek, A. Jurasek, and J. Kovac, *Collect. Czech. Chem. Commun.,* 1980, **49**, 1581.