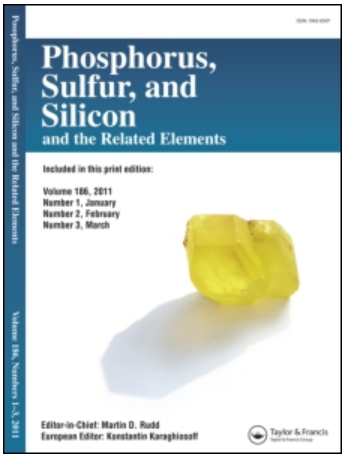

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Reactions with 2-Thiothymine; Selective Cyclization of S-Substituted 2-Thiothymine

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REACTIONS WITH 2-THIOTHYMINE; SELECTIVE CYCLIZATION OF S-SUBSTITUTED 2-THIOTHYMINE

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2-Thiothymine (I) undergoes S-alkylation when treated with some halo compounds such as methyl and ethyl iodides. The S-alkyl derivatives ***II*** *are treated with hydrazine hydrate to produce the hydrazine derivative* ***III****, which condensed with p-chlorobenzaldehyde to give p-chlorobenzaldehydepyrimidinehydrazone derivative* ***IV****. Compound* $\mathbf{II_a}$ *reacts with phosphorus oxychloride to give 4-chloro derivative* ***V****. The chlorine atom in* ***V*** *undergoes nucleophilic substitution with p-chloroaniline and anthranilic acid to produce drivatives* $\mathbf{VI_{a,b}}$*. Dehydrative cyclization of* $\mathbf{VI_b}$ *yields the pyrimido[6,1-b]quinazolin-10-one derivative* ***VII****. Treatment of* ***V*** *with ammonia solution gives the diamino derivative* $\mathbf{VI_d}$*. Reaction of* ***V*** *with sodium azide produces the tetrazolo[1,5-c]pyrimidine derivative* ***VIII****. Compound* ***I*** *undergoes S-alkylation with α-haloketones followed by cyclization to produce the thiazolo[3,2-a]pyrimidine derivatives* $\mathbf{X_{a–c}}$*. Reaction of* ***I*** *with bromomalononitrile produces thiazolo[3,2-a]pyrimidine-2-carbonitrile derivative* ***XII****. Treatment of* ***XII*** *with formic acid, formamide and ammonium thiocyanate produces thiazolo[3,2-a:4,5-d]dipyrimidine derivatives* $\mathbf{XIII_{a–c}}$*. Finally, reacting* ***XII*** *with malononitrile yields ppyrido[2′,3′:4,5]thiazolo[3,2-a]pyrimidine-3-carbonitrile derivative* ***XIV****.*

Keywords: 2-Thiothymine; active chloro derivative; nucleophilic substitution; pyridothiazolopyrimidine; pyrimidoquinazoline; tetrazolopyrimidine; thiazolodipyrimidine; thiazolopyrimidine

In spite of the fact that much literature is published on 2-thiouracil, very few communications are published regarding 2-thiothymine. Only one of these publications discussed chemical reactions of 2-thiothymine.[1] All the others reported its uses in the formation of nucleosides[2–6] and as anti-HIV agents.[7,8]

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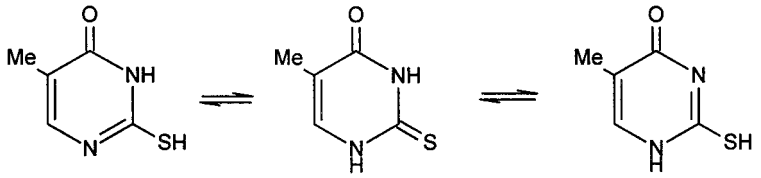
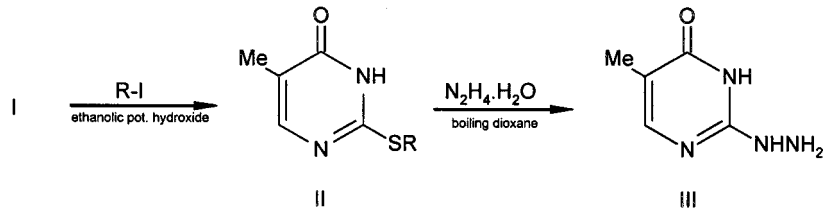
Because of its potential biological importance and the lack of work published dealing with its chemistry, we would like here to report some reactions of 2-thiothymine as well as its uses as a precursor for the synthesis of some biologically important bi- and tricyclic fused heterocycles such as thiazolopyrimidine and thiazolodipyrimidine derivatives.

2-Thiothymine(I) was synthesized after a method published in 1910[9] by formylation of ethyl propionate with ethyl formate in presence of sodium metal. The produced ethyl 2-formylpropionate underwent cyclocondensation with thiourea to give **I**.



I

Compound **I** undergoes S-alkylation when it is treated with some halo compounds. Thus, treatment of I with methyl or ethyl iodide yielded the corresponding S-alkyl derivatives $\mathbf{II_{a,b}}$ respectively. That alkylation took place at the sulphur atom could be proved by reacting each of $\mathbf{II_{a,b}}$ with hydrazine hydrate in boiling dioxane to produce, the same sulphur free compound, 2-hydrazino derivative **III**.



II III

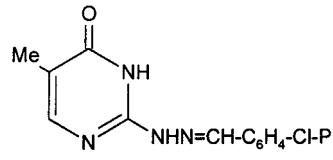
a, R=CH_3

b, R=C_2H_5

Analytical, IR, and ^{1}H-NMR spectral data are in agreement with the proposed structure **II**. The hydrazino derivative **III** displayed IR absorption bands at 3321, 3205, 3151 cm^{-1} (NH_2 and NH) and 1685 (CO). Its ^{1}H-NMR spectrum (DMSO-d_6) showed signals at δ 1.77 ppm (s, 3H, CH_3), 4.48 (s, 2H, NH_2, D_2O exchangeable), 7.39 (s, 1H, pyrimidine

H6), 8.26 (s, 1H, NH, D_2O exchangeable), and 8.65 (bs, 1H, NH, D_2O exchangeable).

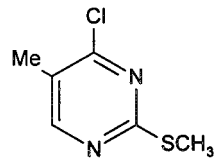
The hydrazino derivative **III** condensed with p-chlorobenzaldehyde to give the p-chlorobenzaldehydepyrimidylhydrazone derivative **IV**. Analytical and spectral data of **IV** are in agreement with the proposed structure (Experimental).



IV

The S-methyl derivative $\mathbf{II_a}$, containing only one active hydrogen atom, reacts smoothly with phosphorus oxychloride, in dry dioxane, to give 4-chloro-5-methyl-2-methylthiopyrimidine (**V**), which gave compatible elemental analyses. Its IR spectrum revealed the disappearance of both NH and CO groups.

The chlorine atom at position 4 in compound **V** shows high activity towards some nucleophiles.



V

Thus, reaction of **V** with some weak nucleophiles such as aromatic amines, namely, p-chloroaniline and anthranilic acid yielded the 4-(p-chlorophenylamino)- and the 4-(o-carboxyphenylamino)pyrimidine derivatives $\mathbf{VI_{a,b}}$.

Compound $\mathbf{VI_a}$ gave compatible elemental analyses and IR data. The ^{1}H-NMR spectrum (DMSO-d_6) of $\mathbf{VI_a}$ showed signals at δ 2.14 ppm (s, 3H, CH_3), 2.41 (s, 3H, SCH_3), 7.37 (d, 2H, aromatic protons), 7.74 (d, 2H, aromatic protons), 8.01 (s, 1H, pyrimidine H_6), and 8.63 (s, 1H, NH, D_2O exchangeable). The IR spectrum of VI_b displayed absorption bands at 3200–2800 cm^{-1} (br, OH + NH) and 1685 (CO). The mass spectrum of $\mathbf{VI_b}$ showed the molecular ion peak at m/z 275 (100%).

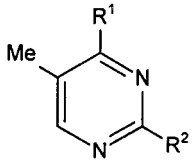
Compound **VI$_b$** underwent cyclization by dehydration upon fusion at 270°C to produce 4-methyl-1-methylthio-10H-pyrimido[6,1-b]quinazolin-10-one (**VII**). The IR spectrum of **VII** revealed the disappearance of any absorption bands at 3200–2800 cm^{-1}, except for the expected —OH absorption (Experimental). Its mass spectrum showed the molecular ion peak at m/z 257 (100%).

Compound V undergoes nucleophilic substitution with thioglycolic acid to produce 2-methylthio-5-methylpyrimidine-4-ylthioacetic acid (**VI$_c$**), which displayed IR absorption bands at 3200–2900 cm^{-1} (br, OH) and 1690 (CO).

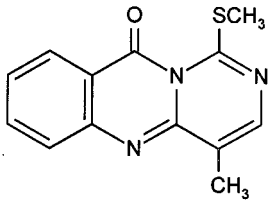
Diaminopyrimidines are known in literature to have biological activity.[10–12] Therefore, we tried to synthesize a pyrimidine derivative containing two amino groups. Thus, treatment of **V** with concentrated ammonia solution (strong nucleophile) resulted in replacement of both chlorine atom at 4-position, and the methylthio group at 2-position, to produce 5-methylpyrimidine-2,4-diamine (**VI$_d$**) in poor yield.

The produced diaminopyrimidine derivative **VI$_d$** displayed IR absorption bands at 3330–3170 cm^{-1} (NH_2). Its ^{1}H-NMR spectrum (DMSO-d_6) showed signals at δ 1.82 ppm (s, 3H, CH_3), 3.43 (s, 2H, NH_2, D_2O exchangeable), 4.45 (s, 2H, NH_2, D_2O exchangeable), and 7.53 (s, 1H, pyrimidine H_6).

Similarly, compound **V** reacted with hydrazine hydrate in boiling dioxane and gave the corresponding 2,4-dihydrazino derivative **VI$_e$**. Analytical, IR, and ^{1}H-NMR spectral data are in agreement with the proposed structure **VI$_e$** (Experimental).



VI



VII

a, R^1 = NH-C_6H_4-Cl-p, R^2 = SCH_3

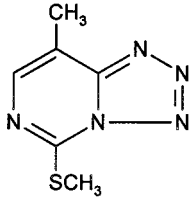
b, R^1 = NH-C_6H_4-COOH-o, R^2 = SCH_3

c, R^1 = SCH_2COOH, R^2 = SCH_3

d, R^1 = R^2 = NH_2

e, R^1 = R^2 = $NHNH_2$

Compound **V** reacted with sodium azide in dimethyl-formamide to produce 8-methyl-5-methylthiotetrazolo[1,5-c]pyrimidine (**VIII**).



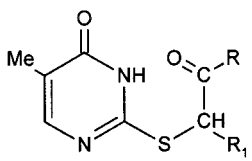
VIII

The mass spectrum of **VIII** revealed the molecular ion peak at m/z 181 (82.9%) and the base peak at m/z 86.

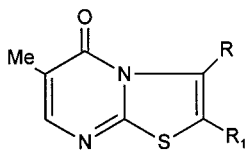
In continuation, alkylation of **I** with α-haloketones yielded the corresponding S-alkylated derivatives. Thus, treatment of **I** with each of chloroacetone, phenacyl bromide, and 3-chloropentan-2,4-dione in ethanolic sodium ethoxide solution yielded the corresponding S-acetonyl-, S-phenacyl-, and S-diacetylmethyl derivatives $\mathbf{IX_{a-c}}$ respectively.

Compounds $\mathbf{IX_{a-c}}$ gave compatible data in elemental analyses, IR and ^{1}H-NMR spectra (Experimental).

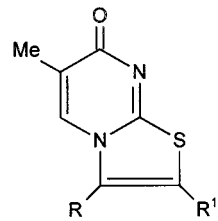
Dehydration of $\mathbf{IX_{a-c}}$ by polyphosphoric acid gave the corresponding substituted thiazolo[3,2-a]pyrimidine derivatives $\mathbf{X_{a-c}}$, respectively, rather than the isomeric structure **X′**.



IX



X



X′

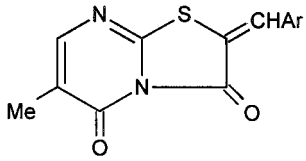
a, R = CH_3 , R_1 = H
b, R = C_6H_5 , R_1 = H
c, R = CH_3 , R_1 = $COCH_3$

The IR spectra of compounds **X** showed the absence of any absorption bands in the NH region and absorptions near 1640 cm^{-1} (CO). The ^{1}H-NMR spectrum of $\mathbf{X_a}$, as an example, showed signals at δ 1.95 ppm (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 6.94 (s, 1H, thiazole H_5), and 8.02

(s, 1H, pyrimidine H_6). The mass spectrum of $\mathbf{X_a}$ showed the molecular ion peak at m/z 180 (100%).

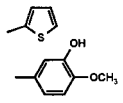
Preferring structure **X** over **X′** was based on ^{1}H-NMR studies (see later).

Furthermore, compound **I** was treated with a mixture of chloroacetic acid, acetic anhydride, and the proper aromatic aldehyde, in acetic acid containing anhydrous sodium acetate, to produce the 2-arylidene thiazolo[3,2-a]pyrimidinedione derivatives $\mathbf{XI_{a–d}}$.



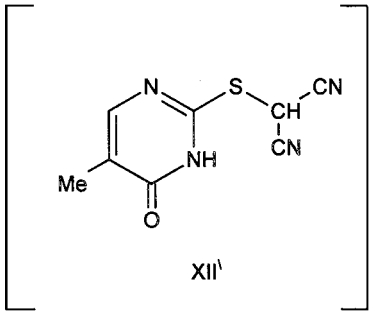
XI

a, Ar = -C_6H_4-Cl-p
b, Ar = -C_6H_4-OCH_3-p
c, Ar =
d, Ar =

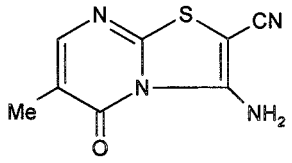


Analytical, IR, and ^{1}H-NMR spectral data are in agreement with the proposed structure **XI**.

Reaction of compound **I** with monobromomalononitrile, in alcoholic potassium hydroxide, produced 3-amino-6-methyl-5-oxo-thiazolo[3,2-a] pyrimidine-2-carbonitrile (**XII**), most probably via the formation of **XII′**.



XII′

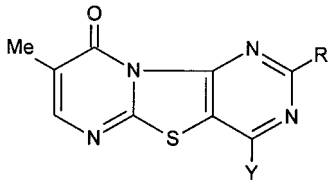


XII

The IR spectrum of compound **XII** displayed absorption bands at 3354, 3301 cm^{-1} (NH_2), 2200 (CN), and 1674 (CO). Its ^{1}H-NMR (DMSO-d_6) showed signals at δ 1.90 ppm (s, 3H, CH_3), 7.81 (s, 1H,

pyrimidine H_7), and 8.50 (s, 2H, NH_2, D_2O exchangeable). The mass spectrum of **XII** showed the molecular ion peak at 206 (100%).

The presence of the enaminonitrile moiety in compound **XII** could be proved by its reactions with each of formic acid, formamide and ammonium thiocyanate to produce thiazolo[3,2-a:4,5-d]dipyrimidine derivatives $\mathbf{XIII_{a-c}}$ respectively.

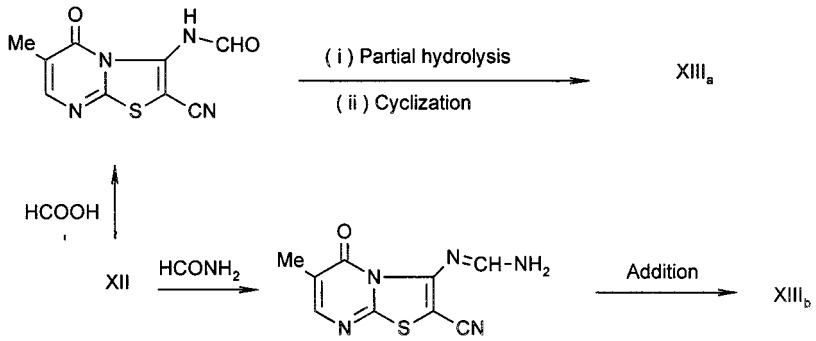


XIII

a, R = H, Y = OH
b, R = H, Y = NH_2
c, R = SH, Y = $NHCSNH_2$

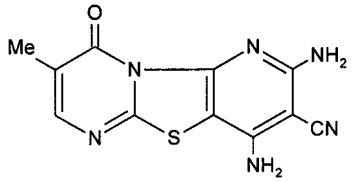
Agreeable analytical and spectral data are obtained for **XIII** (Experimental).

Reactions of **XII** with formic acid and formamide may be take place as shown in Scheme 1.



SCHEME 1

Ultimately, compound **XII** reacted with malononitrile in ethanol containing a catalytic amount of piperidine to yield 2,4-diamino-8-methyl-9-oxopyrido[2′,3′:4,5]Thiazolo[3,2-a]pyrimidine-3-carbonitrile (**XIV**). Analytical and spectral data of **XIV** are in agreement with the proposed structure (Experimental).



XIV

Structure **X** could be preferred over **X′** by comparing chemical shifts (δ) of pyrimidine H-6 proton in $\mathbf{II_{a,b}}$ (7.72 ppm) with those for each of the cyclized products $\mathbf{X_a}$ (8.02 ppm), $\mathbf{XI_b}$ (7.72 ppm), **XII** (7.81 ppm), and $\mathbf{XIII_b}$ (7.81 ppm). It is clear that δ values for H-7 proton in the cyclized structures **X**, **XI**, **XII**, and **XIII** did not suffer from any significant changes from the pyrimidine H-6 in the open structure **II** (difference is within 0.3 ppm). We previously reported[13] that in pyrimidines, cyclization involving a certain nitrogen atom causes a high field shift for its neighboring proton by a value of >1 ppm, whereas cyclization involving the other nitrogen atom would not affect δ value of the same proton. Consequently, we could conclude that cyclization reactions carried out in this article involves N-3 rather than N-1 and thus sructure **X** and the related cyclized products could be preferred.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded (KBr) on a Pye Unicam SP-1000 spectrophotometer. ^{1}H-NMR were obtained with a Varian ^{1}H-Gemini 200 spectrometer and chemical shifts are expressed in δ (ppm) using TMS as the internal standard. The elementary analyses were performed by the Microanalytical Data Center, Cairo University, Egypt.

Compounds **I** were prepared according to literature procedure.[9]

2-Alkylthio-3,4-dihydro-5-methylpyrimidin-4-ones $\mathbf{II_{a,b}}$

A mixture of an equimolar amounts of **I** (1.42 g, 0.01 mmol), alkyliodide and potssium hydroxide (0.65 g, 0.01 mmol) in 30 ml absolute ethanol was heated under reflux for 2 h, cooled, and then poured into water (70 ml). The precipitated solid was collected and crystallized from dioxane to give **IIa**,**b**. Compound IIa was obtained in 90% yield; m.p. 247°C; IR spectrum: 3136 cm^{-1} (NH), 2974 (CH), and 1652 (CO). ^{1}H-NMR spectrum (DMSO-d_6): δ 1.85 ppm (s, 3H, CH_3), 2.11 (s, 3H, SCH_3), 3.55 (bs, 1H, NH, D_2O exchangeable), and 7.72 (s, 1H, pyrimidine H_6).

Analysis: $C_6H_8N_2OS$ (156.31). Requires: C, 46.10; H, 5.15; N, 17.99; S, 20.51%. Found: C, 46.1; H, 5.1; N, 17.8; S, 20.4%.

Compound **II$_b$** was obtained in 85% yield; m.p. 185°C; IR spectrum: 3145 cm^{-1} (NH), 2980 (CH), and 1650 (CO). ^{1}H-NMR (DMSO-d_6): δ 1.26 ppm (t, 3H, CH_3), 1.85 (s, 3H, CH_3), 4.20 (q, 2H, CH_2), 4.52 (bs, 1H, NH, D_2O exchangeable), and 7.72 (s, 1H, pyrimidine H_6). Analysis: $C_7H_{10}N_2OS$ (170.34). Requires: C, 49.35; H, 5.91; N, 16.51; S, 18.86%. Found: C, 49.3; H, 5.8; N, 16.5; S, 18.9%.

3,4-Dihydro-2-hydrazino-5-methylpyrimidin-4-one (III)

A mixture of each of **II$_{a,b}$** (0.01 mmol) and hydrazine hydrate (1.5 ml, 0.03 mmol) in dioxane (30 ml) was heated under reflux for 5 h, the reaction mixture was poured into cold water, whereby the solid so-precipitated was filtered off, dried, and crystallized from dilute dioxane. The yield of compound **III** was 61%; m.p. 230°C; IR spectrum: 3321, 3205, 3151 cm^{-1} (NH_2 and NH), 2985 (CH), and 1685 (CO). ^{1}H-NMR spectrum (DMSO-d_6): δ 1.77 ppm (s, 3H, CH_3), 4.48 (s, 2H, NH_2, D_2O exchangeable), 7.39 (s, 1H, pyrimidine H_6), 8.26 (s, 1H, D_2O exchangeable), and 8.65 (bs, 1H, NH, D_2O exchangeable). Analysis: $C_5H_8N_4O$ (140.13). Requires: C, 42.85; H, 5.74; N, 39.98%. Found: C, 42.7; H, 5.7; N, 39.9%.

2-(4-Chlorophenyl)methylenehydrazino-3,4-dihydro-5-methylpyrimid-in-4-ones (IV)

A mixture of 0.01 mmol of **III** and an equimolar amount of p-chlorobenzaldehyde in 50 ml of absolute ethanol was refluxed for 3 h, the solid that formed on dilution with water, was collected, dried, and crystallized from acetic acid; m.p. 243°C; IR spectrum: 3310, 3130 cm^{-1} (NH) and 1680 (CO). Analysis: $C_{12}H_{11}ClN_4O$ (262.68). Requires: C, 54.86; H, 4.21; N, 21.32; Cl, 13.49%. Found: C, 54.9; H, 4.2; N, 21.1; Cl, 13.3%.

4-Chloro-5-methyl-2-methylthiopyrimidine (V)

A mixture of **II$_a$** (1.56 g, 0.01 mmol) in dry dioxane (10 ml) and phosphorus oxychloride (2.5 ml) was heated under reflux for 2 h, cooled, and poured into ice. The precipitated solid was collected, dried, and crystallized from methanol to give 1.04 g (60%) of **V**; m.p. 35°C; IR spectrum: 2980 cm^{-1} (CH). Analysis: $C_6H_7ClN_2S$ (174.60). Requires: C, 41.27; H, 4.01; N, 16.04; S, 18.36; Cl, 20.30%. Found: C, 41.3; H, 4.0; N, 16.1; S, 18.2; Cl, 20.3%.

4-(p-Chlorophenylamino)-5-methyl-2-methylthiopyrimidine $VI_{a,b}$

A mixture of **V** (0.01 mmol) and an appropriate primary aromatic amine (0.01 mmol) in dry dioxane (20 ml) was heated under reflux for 1 h, the reaction mixture was poured onto cold water, whereby the solid produced so precipitated was filtered off, dried, and crystallized from dioxane/water.

4-(p-Chlorophenylamino)-5-methyl-2-methylthiopyrimidine (VI_a)

Yield (80%); m.p. 140°C; IR spectrum: 3228 cm^{-1} (NH) and 2975 (CH). ^{1}H-NMR spectrum (DMSO-d_6): δ 2.14 ppm (s, 3H, CH_3), 2.41 (s, 3H, SCH_3), 7.37 (d, 2H, aromatic protons), 7.74 (d, 2H, aromatic protons), 8.01 (s, 1H, pyrimidine H_6), and 8.63 (s, 1H, NH, D_2O exchangeable). Analysis: $C_{12}H_{12}ClN_3S$ (265.75). Requires: C, 54.23; H, 4.54; N, 15.80; S, 12.06; Cl, 13.33%. Found: C, 54.3; H, 4.5; N, 15.7; S, 12.1; Cl, 13.3%.

4-(o-Carboxyphenylamino)-5-methyl-2-methylthiopyrimidine (VI_b)

Yield (80%); m.p. 255°C; IR spectrum: 3200–2800 cm^{-1} (br, OH + NH) and 1685 (CO). ^{1}H-NMR spectrum (DMSO-d_6): δ 2.14 ppm (s, 3H, CH_3), 2.14 (s, 3H, SCH_3), 8.02 (s, 1H, pyrimidine H_6), 8.61 (s, 1H, NH, D_2O exchangeable), and 10.73 (s, 1H, COOH, D_2O exchangeable). Analysis: $C_{13}H_{13}N_3O_2S$ (275.31). Requires: C, 56.71; H, 4.75; N, 15.26; S, 11.65%. Found: C, 56.6; H, 4.7; N, 15.3; S, 11.7%.

4-Methyl-1-methylthio-10H-pyrimido-[6,1-b]quinazoline-10-one (VII)

Compound $\mathbf{VI_b}$ (0.01 mmol) was heated at 270°C on an oil bath for half an hour, the reaction mixture was then triturated with absolute ethanol. The solid product, so formed, was filtered off, dried, and crystallized from dioxane to yield (80%) of **VII**; m.p. 283°C; IR spectrum 1690 cm^{-1} (CO). Analysis: $C_{13}H_{11}N_3OS$ (257.29). Requires: C, 60.68; H, 4.30; N, 16.33; S, 12.46%. Found: C, 60.7; H, 4.2; N, 16.3; S, 12.5%.

4-Carboxymethylthio-5-methyl-2-methylthiopyrimidine (VI_c)

A mixture of **V** (0.01 mmol) and thioglycollic acid (0.01 mmol) in dry dioxane (20 ml) was heated under reflux for 3 h then cooled. The

precipitated solid was collected, dried, and crystallized from dioxane to give (70%) of **VI$_c$**; m.p. 245°C; IR spectrum 3200–2900 cm^{-1} (br, OH) and 1690 (CO). Analysis: $C_8H_{10}N_2O_2S_2$ (230.29). Requires: C, 41.72; H, 4.37; N, 12.16; S, 27.84%. Found: C, 41.7; H, 4.3; N, 12.2; S, 27.9%.

5-Methylpyrimidine-2,4-diamine (VI$_d$)

A mixture of **V** (0.01 mmol) and concentrated ammonia solution was heated under reflux for 2 h, the solid thus formed after evaporation, was collected, dried, and crystallized from ethanol to give (30%) of **VI$_d$**; m.p. 190°C; IR spectrum 3330–3170 cm^{-1} (NH_2). ^{1}H-NMR spectrum (DMSO-d_6): δ 1.82 ppm (s, 3H, CH_3), 3.43 (s, 2H, NH_2, D_2O exchangeable), 4.45 (s, 2H, NH_2, D_2O exchangeable), and 7.53 (s, 1H, pyrimidine H_6). Analysis: $C_5H_8N_4$ (124.13). Requires: C, 48.37; H, 6.48; N, 45.13%. Found: C, 48.4; H, 6,6; N, 45.1%.

2,4-Dihydrazino-5-methylpyrimidine (VI$_e$)

A mixture of **V** (0.01 mmol) and Hydrazine hydrate (0.05 mmol) in dioxane (20 ml) was heated under reflux for 5 h, the reaction mixture was evaporated, cooled, whereby the solid so-precipitated was filtered off, dried, and crystallized from water. The yield of compound **VI$_e$** was 60%; m.p. 183°C; IR spectrum 3320–3180 cm^{-1} (NH_2). The ^{1}H-NMR spectrum (DMSO-d_6): δ 1.83 ppm (s, 3H, CH_3), 3.47 (s, 2H, NH_2, D_2O exchangeable), 4.12–4.31 (bs, 3H, $NH_2 + NH$, D_2O exchangeable), 7.35 (s, 1H, NH, D_2O exchangeable), and 7.52 (s, 1H, Pyrimidine H_6). Analysis: $C_5H_{10}N_6$ (154.16). Requires: C, 38.95; H, 6.53; N, 54.51%. Found: C, 38.8; H, 6.5; N, 54.5%.

8-Methyl-5-methylthiotetrazolo[1,5]pyrimidine (VIII)

A mixture of **V** (0.01 mmol) and sodium azide (0.01 mmol) in dimethyl formamide (20 ml) was stirred at room temperature for 12 h, the reaction mixture was heated on a water bath for 1 h, then poured onto ice/water whereby the solid product that precipitated, was filtered off, dried, and crystallized from methanol. Compound **VIII** was obtained in 64% yield; m.p. 100°C; IR spectrum 2950 cm^{-1} (CH). Analysis: $C_6H_7N_5S$ (181.20). Requires: C, 39.76; H, 3.88; N, 38.64; S, 17.69%. Found: C, 39.7; H, 3.8; N, 38.5; S, 17.7%.

Alkylation of I. Preparation of IX$_{a–c}$

A mixture of an equimolar amounts of **I** (0.01 mmol) and an appropriate α-haloketone in ethanolic sodium ethoxide solution (20 ml) was heated,

TABLE I Characterization Data of Compounds $\mathbf{IX_{a–c}}$ and $\mathbf{X_{a–c}}$

Compound	Molecular formula	Yield %	m.p.°C Solvent	Analysis Calc. %C %H %N %S	Analysis Found %C %H %N %S	IR (KBr) cm^{-1}
$\mathbf{IX_a}$	$C_8H_{10}N_2O_2S$ (198.22)	70	195 Ethanol	48.47 5.08 14.13 16.17	48.4 5.1 14.1 16.1	3417, 3008 (NH), 1631 (CO) 1566 (CO)
$\mathbf{IX_b}$	$C_{13}H_{12}N_2O_2$ (260.28)	80	230 Ethanol	59.98 4.64 10.76 12.31	60.0 4.6 10.7 12.3	3421, 3213 (NH), 1685 (CO), 1639 (CO)
$\mathbf{IX_c}$	$C_{10}H_{12}N_2O_3S$ (240.23)	75	190 Ethanol	49.99 5.02 11.65 13.34	49.9 5.0 11.7 13.2	3031 (NH), 1631 (CO), 1587 (CO)
$\mathbf{X_a}$	$C_8H_9N_2OS$ (181.20)	60	196 Dioxane	53.02 5.00 15.45 17.69	53.0 5.0 15.3 17.7	1640 (CO)
$\mathbf{X_b}$	$C_{13}H_{11}N_2OS$ (243.27)	72	262 Dioxane	64.18 4.55 11.51 13.18	64.2 4.5 11.5 13.1	1635 (CO)
$\mathbf{X_c}$	$C_{10}H_{10}N_2O_2S$ (222.24)	58	202 Ethanol	54.04 4.53 12.60 14.42	54.1 4.5 12.6 14.5	1650 (CO), 1642 (CO)

$\mathbf{IX_b}$: ^{1}H-NMR spectrum (DMSO-d_6): δ 1.82 ppm (s, 3H, CH_3), 4.78 (s, 2H, CH_2), 7.30–8.04 (m, 6H, 5 aromatic protons + pyrimidine H_6) and 8.30 (bs, 1H, NH, D_2O exchangeable).

$\mathbf{X_a}$: ^{1}H-NMR spectrum (DMSO-d_6): δ 1.95 ppm (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 6.94 (s, 1H, thiazole H_5) and 8.02 (s, 1H, pyrimidine H_6).

under reflux for 3 h, the reaction mixture was poured onto water, the solid product formed was filtered off, and crystallized from the proper solvent (Table I).

Cyclization of $IX_{a–c}$. Synthesis of $X_{a–c}$

A suspension of 1 g of each of $\mathbf{IX_{a–c}}$ in 10 g of polyphosphoric acid was heated at 100–120°C on an oil bath for 1 h, the solution was left to cool, poured with stirring into ice/water, and basified with

ammonium hydroxide solution. The solid that formed was collected, washed with water, and crystallized from the proper solvent to give $\mathbf{X_{a-c}}$ (Table I).

2-Arylidene Thiazolo[3,2-a]pyrimidinedione $\mathbf{XI_{a-d}}$

A mixture of 0.01 mmol of each of **I** (1.42 g), (1.04 g) of chloroacetic acid, an appropriate aldehyde, and (2 g) of anhydrous sodium acetate was refluxed in 30 ml of glacial acetic acid and 15 ml of acetic anhydride for 3 h, the reaction mixture was poured into water. The precipitate that formed was filtered off, washed with water, dried, and crystallized from the proper solvent to produce $\mathbf{XI_{a-d}}$ (Table II).

3-Amino-6-methyl-5-oxothiazolo[3,2-a]pyrimidine-2-carbonitrile (XII)

A mixture of 0.01 mmol of each of **I** (1.42 g) and monobromomalononitrile was heated under reflux for 1 h in alcoholic potassium hydroxide

TABLE II Characterization Data of Compounds $\mathbf{XI_{a-d}}$

Compound	Molecular formula	Yield %	m.p.°C Solvent	Analysis Calc. %C %H %N %S	Analysis Found %C %H %N %S	IR (KBr) cm^{-1}
$\mathbf{XI_a}$	$C_{14}H_9ClN_2O_2S$ (304.73)	80	280 Acetic acid	55.17 2.97 9.19 10.52	55.0 2.9 9.2 10.6	1720 (CO), 1681 (CO)
$\mathbf{XI_b}$	$C_{15}H_{12}N_2O_3S$ (300.01)	83	290 dilute Acetic acid	59.99 4.02 9.32 10.67	60.0 4.0 9.2 10.7	1684 (CO), 1670 (CO)
$\mathbf{XI_c}$	$C_{12}H_8N_2O_2S_2$ (276.30)	70	340 DMF	52.16 2.91 10.13 23.20	52.1 3.0 10.2 23.1	1715 (CO), 1640 (CO)
$\mathbf{XI_d}$	$C_{15}H_{12}N_2O_4S$ (316.31)	78	305 Acetic acid	56.95 3.81 8.85 10.13	56.9 3.8 8.8 10.1	3340–3210 (OH), 1710 (CO), 1680 (CO)

XI_a: Cl, Requires: 11.63; Found: 11.5%.

XI_b: ^{1}H-NMR spectrum (DMSO-d_6): δ 1.98 ppm (s, 3H, CH_3), 3.89 (s, 3H, CH_3), 7.15–7.74 (q, 4H, aromatic protons), 7.72 (s, 1H, pyrimidine-H_6) and 8.1 (s, 1H, CH).

solution (20 ml). The reaction mixture was poured onto water. The precipitate, thus formed, was filtered off, washed with water, dried, and crystallized from dilut dimethylformamide. Compound **XII** was obtained in 70% yield; m.p. 282°C; IR spectrum 3354, 3301 cm^{-1} (NH_2), 2200 (CN) and 1674 (CO). The ^{1}H-NMR spectrum (DMSO-d_6): δ 1.90 ppm (s, 3H, CH_3), 7.81 (s, 1H, pyrimidine H_7) and 8.50 (s, 2H, NH_2, D_2O exchangeable). Analysis: $C_8H_6N_4OS$ (206.19). Requires: C, 46.59; H, 2.92; N, 27.16; S, 15.54%. Found: C, 46.5; H, 2.9; N, 27.1; S, 15.5%.

8-Methylthiazolo[3,2-a: 4,5-d]dipyrimidine-4,9-dione (XIII$_a$)

A mixture of compound **XII** (1 g) and formic acid (10 ml) was heated under reflux for 10 h, the solid product that separated upon cooling was filtered off and crystallized from dimethyl formamide in 64% yield; m.p. 315°C; IR spectrum 3178 cm^{-1} (NH) and 1670, 1612 (2CO). Analysis: $C_9H_6N_4O_2S$ (234.15). Requires: C, 46.16; H, 2.56; N, 23.92; S, 13.69%. Found: C, 46.2; H, 2.6; N, 23.8; S, 13.5%.

4-Amino-8-methylthiazolo[3,2-a: 4,5-d]dipyrimidine-9-one (XIII$_b$)

A mixture of compound **XII** (1 g) and formamide (10 ml), in presence of formic acid (5 ml) and dimethyl formamide (5 ml), was heated under reflux for 6 h, the solid product that separated upon cooling was filtered off and crystallized from dilute dimethyl formamide in 58% yield; m.p. 340°C; IR spectrum 3269, 3039 cm^{-1} (NH) and 1660 (CO). ^{1}H-NMR spectrum (DMSO-d_6): δ 1.86 ppm (s, 3H, CH_3), 3.41 (s, 2H, NH_2, D_2O exchangeable), 7.21 (s, 1H, Pyrimidine H_2), and 7.81 (s, 1H, Pyrimidine H_7). Analysis: $C_9H_7N_5OS$ (233.21). Requires: C, 46.34; H, 3.01; N, 30.02; S, 13.74%. Found: C, 46.3; H, 2.9; N, 30.0; S, 13.6%.

Reaction of XII with Ammonium Thiocyanate. Preparation of XIII$_c$

A mixture of **XII** (1 g) and an excess amount of ammonium thiocyanate (3 g) was heated under reflux for 6 h in acetic acid (20 ml). The reaction mixture poured onto ice/water; the solid that separated was filtered off, dried, and crystallized from dilute dimethyl formamide, in 48% yield; m.p. 330°C; IR spectrum 3309, 3163 cm^{-1} (NH) and 1643 (CO). Analysis: $C_{10}H_8N_6OS_2$ (292.30). Requires: C, 41.09; H, 2.75; N, 28.74; S, 21.93%. Found: C, 41.0; H, 2.6; N, 28.7; S, 21.8%.

2,4-Diamino-8-methyl-9-oxopyrido[2′,3′:4,5]thiazolo-[3,2-a]pyrimidine-3-carbonitrile (XIV)

A mixture of (0.01 mmol) of each of **XII** and malononitrile was heated under reflux for 2 h in ethanol (20 ml) containing 3 drops of piperidine. The reaction mixture poured onto water; the solid so formed, was filtered off, dried, and crystallized from dilute dimethyl formamide, in 60% yield; m.p. 260°C; IR spectrum 3280, 3160 cm^{-1} (NH_2), 2230 (CN) and 1650 (CO). Analysis: $C_{11}H_8N_6OS$ (272.25). Requires: C, 48.52; H, 2.95; N, 30.86; S, 11.77%. Found: C, 48.5; H, 2.9; N, 30.8; S, 11.7%.

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