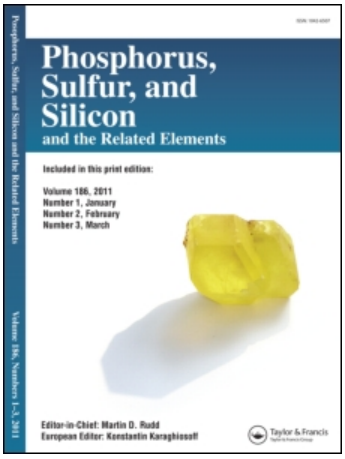

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Synthesis of Thiazolo[5,4-*d*]pyrimidine, Thiazolo[5,4-*b*]pyridine, Thiazolo[4,5-*b*]pyrrolizine and Thiazolo[5,4-*d*]thiazaphosphinine

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5-amino-2-methylsulfanyl-thiazole-4-carboxylic acid ethyl ester ***1*** *reacted with malononitrile, benzoylisothiocyanate, and 2-(methylsulfanyl-phenylaminomethylene)malononitrile to furnish the thiazolopyrimidine-2-one derivatives* ***2–4****, respectively.* ***1*** *reacted with the dipotassium salt of the 2-dimercaptomethylene-malononitrile prepared by the reaction of malononitrile and* CS_2 *and KOH in the presence of TBAB under solid–liquid phase transfer catalysis to give* ***5****. Reacting* ***1*** *with triethyl orthoformate, chloroacetyl chloride, and 2,5 dimethoxy tetrahydrofuran afforded* ***6–8****. The reaction of* ***1*** *with Lawesson's reagent gave* ***9****. The reaction of* ***1*** *with benzylidinemalononitrile gave* ***10****. The reaction of hydrazine hydrate with* ***1*** *and/or* ***6*** *afforded* ***11*** *and* ***12****, respectively.* ***7*** *reacted with malononitrile to give* ***13****. The cyclization of* ***8*** *by the action of PPA gave* ***14****. Thiazole-4-carbohydrazide* ***11*** *reacted with acetic anhydride/acetic acid mixture and with formic acid to yield* ***15*** *and* ***16****, respectively.* ***11*** *reacted with* p*-chloro benzaldehyde to give* ***17****. The treatment of compound* ***17*** *and/or* ***11*** *with triethyl orthoformate afforded* ***18*** *and* ***19****, respectively. The reaction of* ***11*** *with* CS_2 *and with 2-(bismethylsulfanyl-methylene)malononitrile gave* ***20*** *and* ***21****, respectively.*

Keywords 5-amino-2-methylsulfanyl-thiaozle-4-carboxylic acid ethyl ester; thiazolopyridine; thiazolopyrimidines; thiazolothiazaphosphinine

INTRODUCTION

The value of the thiazolopyrimidine ring system as an antipurine and hence its importance as an anticancer agent has been previously recognized.[1] Thiazolopyrimidines have wide antimicrobial activities including bacteriostatic, antifungal, antiprotozoal, and antischistosomal activities.[2–4] As well, several thiazolo[5,4-d]pyrimidine

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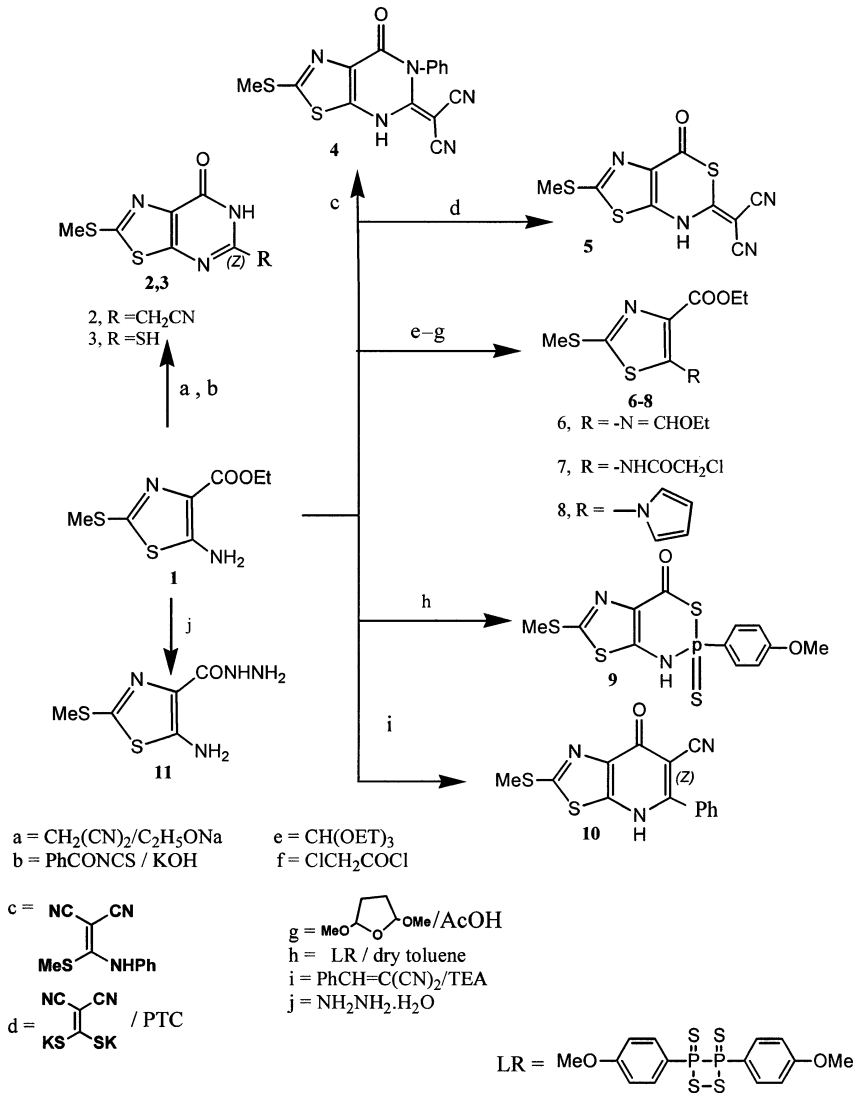
derivatives have been synthesized and found to possess molluscicidal properties.[5–8] Therefore, in view of these observations and as a continuation of our previous work,[9–11] we wish to report herein the synthesis of some new heterocyclic compounds containing a thiazole moiety fused with pyrimidine, pyridine, thiazine, pyrrolizine, and thiazaphosphinine nuclei.

RESULTS AND DISCUSSION

The reaction of 5-amino-2-methylsulfanyl-thiazole-4-carboxylic acid ester ethyl (**1**) with malononitrile in ethanol and sodium ethoxide as a basic catalyst gave (2-methylsulfanyl-7-oxo-6,7-dihydro-thiazolo [5,4-d]pyrimidin-5-yl)-acetonitrile (**2**) (Scheme 1). When the amino ester **1** reacted in situ with benzoyl isothiocyanate in the presence of KOH, it afforded 5-mercapto-2-methylsulfanyl-6*H*-thiazolo[4,5-d]pyrimidin-7one (**3**). The IR spectral data of product **3** showed no bands characteristic for a benzoyl carbonyl group, confirming that debenzoylation has taken place during the course of the cyclization reaction. The reaction of **1** with 2-(methylsulfanyl-phenylaminomethylene)-malononitrile gave 2-(2-meth-ylsulfanyl-7-oxo-6-phenyl-6,7-dihydro-4*H*-thiazolo[5,4-d]pyrimidin-5-yl-idene)malononitrile (**4**) (Scheme 1). When the amino ester **1** reacted with a dipotassium salt of 2-dimercaptomethylene-malononitrile prepared by the reaaction of malononitrile with CS_2 and KOH using Tetra Butylamonium Bromide (TBAB) under solid-liquid phase transfer catalysis, it gave 2-(2-methylsulfanyl-7-oxo-4,7-dihydro-thiazolo[5,4-d][1,3]thiazin-5-yli-dene)-malononitrile (**5**) (Scheme 1). The IR spectrum of **5** showed an absorption band at 2220 cm^{-1} corresponding to the CN group. The condensation of **1** with triethyl orthoformate[12] in boiling acetic anhydride afforded the corresponding ethyl 5-ethoxymethyleneamino-2-methylsulfanyl-thiazole-4-carboxylic acid ethyl ester (**6**) (Scheme 1). The treatment of **1** with chloroacetyl chloride,[13] led to the formation of 5-(chloroacetylamino)-2-methylsulfanyl-thiazole-4-carboxylic acid ethyl ester (**7**) (Scheme 1).

2-methylsulfanyl-5-pyrrol-1-yl-thiazole-4-carboxylic acid ethyl ester (**8**) has been yielded when **1** was allowed to react with 2,5-dimethoxytetrahydrofuran in refluxing acetic acid.

The chemistry of Lawesson's Reagent (LR) as a thiation reagent has been studied, and several papers describe its ring-closure reactions with substrates containing two functional groups.[9,10,14] So, the reaction of compound **1** with LR in boiling toluene yielded the 2-(4-methoxyphenyl)-6-(methylsulfanyl)-1,2-dihydro-4H-[1,3]thiazolo [5,4-d][1,3,2]thiazaphosphinin-4-one 2-sulfide (**9**) (Scheme 1). The IR



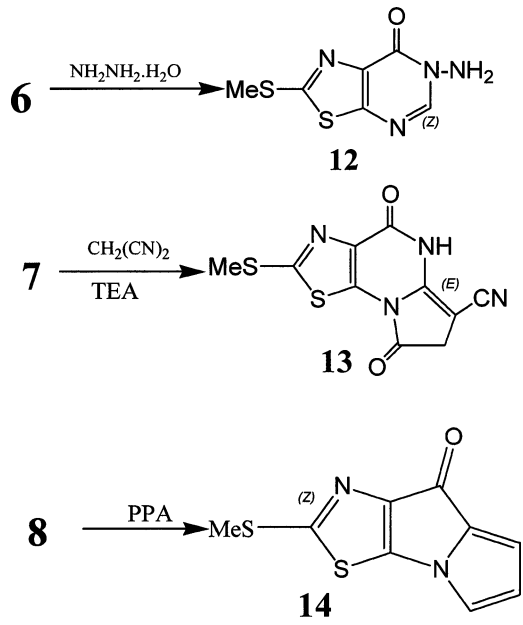
SCHEME 1

spectrum of **9** showed absorption bands at 3390 cm^{-1}, 1690 cm^{-1}, and 1045 cm^{-1} for NH, C=O, and P=S groups, respectively.

Upon reacting the amino ester **1** with benzylidenemalononitrile in boiling dioxane using TEA as a basic catalyst, the corresponding 2-methylsulfan-yl-7-oxo-5-phenyl-4,7-dihydrothiazolo[5,4-b]pyridine-6-carbonitrile (**10**) was afforded and hydrogen cyanide molecule was expelled.[15]

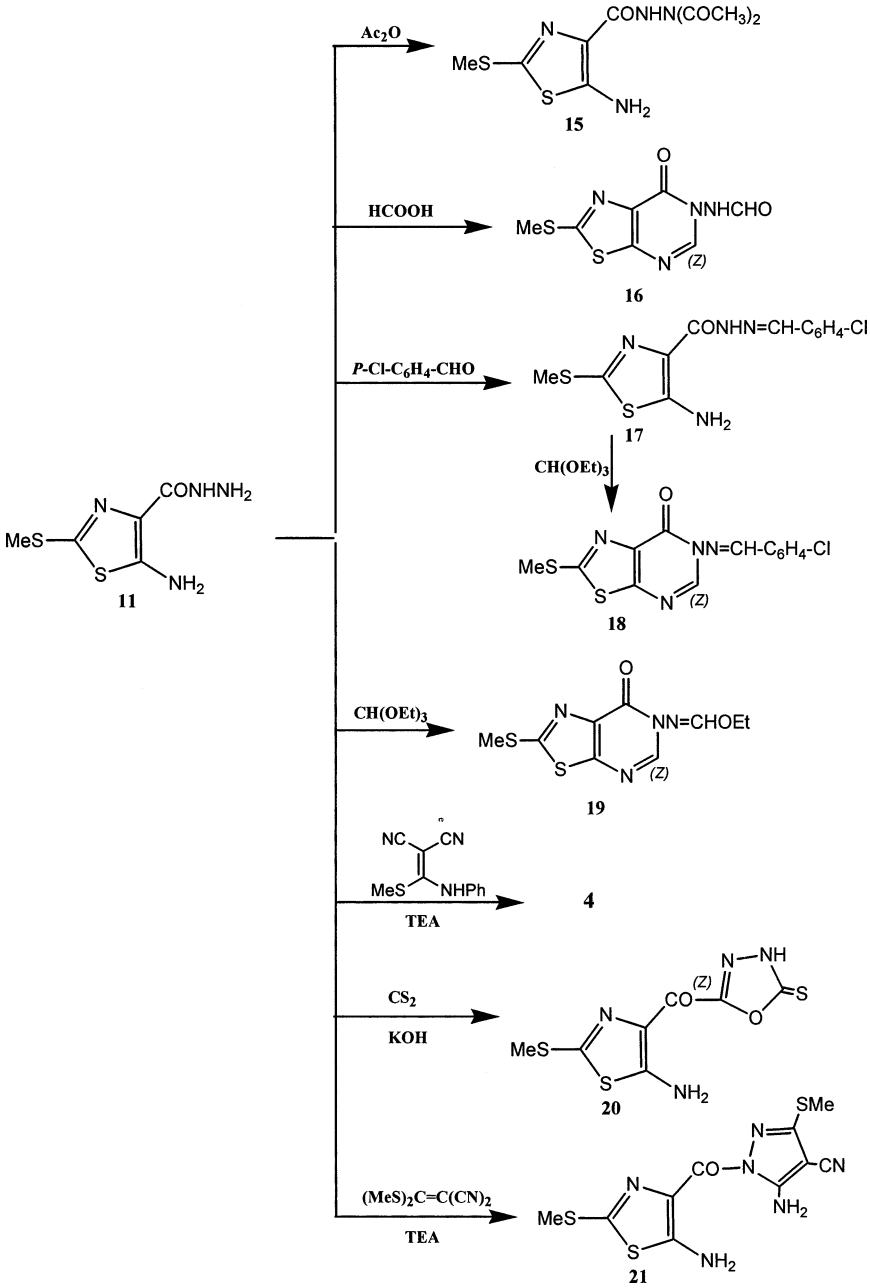
5-amino-2-methylsulfanyl-thiazole-4-carbohydrazide (**11**) was obtained when the amino ester **1** was allowed to heat under reflux with hydrazine hydrate for 8 h (Scheme 1).

Compounds **6–8** have been utilized as key intermediates to produce di- and tricyclic fused systems. Thus, reacting compound **6** with hydrazine hydrate in boiling ethanol afforded 6-amino-2-(methylsulfanyl)-thiazolo[5,4-d]pyrimidin-7(6*H*)one (**12**); reacting **7** with malononitrile[16] in dioxane in presence of TEA for 1 h gave 2-(methylsulfanyl)-4,8-dioxo-4,5,7,8-tetrahydropyrrolo[1,2-a]-thiazolo-[5,4-e]pyrimidine-6-carbonitrile (**13**), and boiling **8** in PPA yielded 2-methylsulfanyl-8*H*-thiazolo [4,5-b]pyrrolizin-8-one (**14**) (Scheme 2).



SCHEME 2

A series of reactions on the amino carbohydrazide **11** with some reagents has been performed. Thus, boiling **11** in a mixture of acetic anhydride/acetic acid and in formic acid gave 5-amino-2-methylsulfanyl-thiazole-4-carboxylic acid N,N-diacetylhydrazide (**15**) and N-(2-methylsulfanyl-7-oxo-7H-thiazolo[5,4-d]pyrimidin-6-yl)-formamide (**16**), respectively (Scheme 3). The condensation of **11** with *p*-chlorobenzaldehyde in the presence of piperidine as a basic catalyst gave the chlorophenyl carbohydrzide derivative (**17**).



SCHEME 3

When **17** and or **11** were boiled in triethyl orthoformate,[17] they gave 6-(benzylideneamino)-2-(methylsulfanyl)[1,3]thiazolo[5,4-d]pyrimidin-7(6 H)one (**18**) and ethyl 2-(methylsulfanyl)-7-oxo[1,3]thiazolo[5,4-d] pyr imidin-6(7H)ylimidoformate (**19**), respectively (Scheme 3).

The reaction of **11** with 2-(methylsulfanyl-phenylaminomethylene) malononitrile in presence of TEA gave a compound identical with that obtained from the reaction of **1** with the same reagent identified as 2-(2-methylsulfanyl-7-oxo-6-phenyl-6,7-dihydro-4*H*-thiazolo-[5,4-d]pyrimidin-5-ylidene)malononitrile (**4**).

When compound **11** was subjected to react with carbon disulfide[18,19] in the presence of KOH, the (5-amino-2-methylsulfanyl-thiazol-4-yl)-(5-thioxo-4,5-dihydro-[1,3,4]oxadizol-2-yl)-methanone **20** was produced.

Finally, treating compound **11** with 2-(bis-methylsulfanyl-methylene) malononitrile in the presence of TEA gave 5-amino-1-(5-amino-2-methysul-fanyl-thiazole-4-yl-carbonyl)-3-methylsulfanyl-1*H*-pyrazole-4-carbonitrile (**21**) (Scheme 3).

EXPERIMENTAL

All melting points were determined on a Koffler melting points apparatus and are uncorrected. IR spectra were recorded on a Nicolet 710 FT-IR spectrometer in K Br discs. ^{1}H-NMR spectra were recorded on a Varian EM 390 at 90 MHz using TMS as an internal reference. Elemental analyses were carried out at the Microanalytical Center of Cairo University (Egypt). Compound **1** was prepared according to the literature.[20]

Synthesis of Compound 2

To a mixture of compound **1** (0.02 mol) and malononitrile (0.02 mol) in ethanol (30 mL), sodium ethoxide (0.46 g sodium in 5 mL ethanol) was added. The reaction mixture was refluxed for 1 h; the product was collected by filteration, washed with water, dried, and crystallized from the proper solvent (Table I). IR $\nu_{max:}$ 3320(NH), 2225(CN), 1690(CO), 1600(C=N). ^{1}H-NMR (DMSO-d_6) δ: 2.3 (s, 3H, SCH_3), 4.5 (s, 2H, CH_2), 9.4 (s, 1H, NH).

Synthesis of Compound 3

To a mixture of compound **1** (0.02 mol) and KOH (0.025 mol) in ethanol (20 mL), benzoylisothiocyanate (0.02 mol) was added. The reaction mixture was stirred for 6 h at 40°C, cooled at r.t., and then poured into ice water (200 mL) and acidified with HCl (10 mL). The solid that

TABLE I Analytical Data of the Synthesized Compounds

Compound no.	Yield	Solvent cryst.	M.P. [°C]	Mol. formula (Mol. Wt.)	Elemental Analyses Calcd./Found [%] C%	H%	N%
2	54	Ethanol	261	$C_8H_6N_4OS_2$	40.32	2.54	23.51
				(238.29)	40.60	2.74	23.80
3	86	Ethanol	231	$C_6H_5N_3OS_3$	31.15	2.18	18.17
				(231.32)	31.40	2.32	17.90
4	50	Dioxane	>300	$C_{15}H_9N_5OS_2$	53.08	2.67	20.63
				(339.40)	53.28	2.70	20.30
5	70	Ethanol	210	$C_9H_4N_4OS_3$	38.56	1.44	19.98
				(280.35)	38.81	1.77	19.55
6	74	Ethanol	167	$C_{10}H_{14}N_2O_3S_2$	43.78	5.14	10.21
				(274.36)	43.28	5.46	10.11
7	50	Ethanol	149	$C_9H_{11}ClN_2O_3S_2$	36.67	3.76	9.50
				(294.78)	37.07	3.77	9.70
8	60	Ethanol	188–190	$C_{11}H_{12}N_2O_2S_2$	49.23	4.51	10.44
				(268.36)	48.80	4.55	10.86
9	77	Ethanol	231–232	$C_{12}H_{11}N_2O_2S_4P$	38.49	2.69	7.48
				(374.74)	38.78	3.01	7.58
10	80	Ethanol	277–279	$C_{14}H_9N_3OS_2$	56.17	3.03	14.04
				(299.37)	56.55	3.25	14.10
11	72	Ethanol	170	$C_5H_8N_4OS_2$	29.40	3.95	27.43
				(204.28)	29.70	4.12	27.11
12	54	Benzene	200	$C_6H_6N_4OS_2$	33.63	2.82	26.51
				(214.27)	34.03	2.66	26.22
13	30	Acetic acid	>300	$C_{10}H_6N_4O_2S_2$	43.16	2.17	20.13
				(278.31)	43.56	2.32	20.41
14	41	Dioxane	>300	$C_9H_6N_2OS_2$	48.63	2.72	12.60
				(222.29)	49.02	2.77	12.90
15	77	Ethanol	160–61	$C_9H_{12}N_4O_3S_2$	37.49	4.19	19.42
				(288.35)	37.56	4.32	19.03
16	66	Dioxane-H_2O (3:1)	>300	$C_7H_6N_4O_2S_2$	34.70	2.50	23.12
				(242.70)	35.05	2.67	22.88
17	64	Ethanol	210–212	$C_{12}H_{11}ClN_4OS_2$	44.10	3.39	17.10
				(326.83)	44.15	3.80	17.03
18	58	Dioxane-H_2O (1:1)	220–221	$C_{13}H_9ClN_4OS_2$	46.36	2.69	16.63
				(336.82)	46.78	2.85	16.93
19	61	Ethanol	185–187	$C_9H_{10}N_4O_2S_2$	39.99	3.73	20.72
				(270.33)	40.34	3.83	20.80
20	44	Ethanol	220	$C_7H_6N_4O_2S_3$	30.65	2.20	20.42
				(274.35)	31.05	2.27	20.82
21	50	Benzene	>300	$C_{10}H_{10}N_6OS_3$	36.79	3.09	25.75
				(326.42)	37.12	3.11	25.65

separated was collected by filtration, washed with water, dried and crystallized from the proper solvent (Table I). IR, ν_{max}: 3240(NH), 2765(SH), 1680(CO), 1600(C=N). ^{1}H-NMR (DMSO-d_6), δ: 1.3 (s, 1H, SH), 2.3 (s, 3H, SCH_3), 8.0 (s, 1H, NH).

Synthesis of Compound 4

Method A

A mixture of compound **1** (0.002 mol) and 2-(methylsulfanyl-phenylamino-methylene)-malononitrile (0.002 mol) was dissolved in *ter*. butanol (30 mL) containing few drops of triethyl amine as a catalyst. The reaction mixture was heated under reflux until the evolution of MeSH was ceased (12 h) and then evaporated in vacuo. The remaining product was triturated with pet. ether (40–60°C), and the residual solid was collected by filtration and crystallized from the proper solvent (Table I). IR, $\nu_{max:}$ 3220 (NH), 3065 (CH arom.), 2190 (CN), 1690(CO), 1600 (C=N), 670 (P=S). ^{1}H-NMR (DMSO-d_6), δ: 2.3 (s, 3H, SCH_3), 7.6–7.0 (m, 5H, Ar-H), 10.2 (s, 1H, NH).

Synthesis of Compound 4

Method B

A mixture of compound **11** (0.002 mol) and 2-(methylsulfanyl-phenylamino-methylene)-malononitrile (0.002 mol) were dissolved in *ter*. butanol (30 mL) containing drops of triethyl amine as a catalyst. The reaction mixture was heated under reflux until the evolution of MeSH was ceased (12 h) and then evaporated in vacuo. The remaining product was triturated with pet. ether (40–60°C), and the residual solid was collected by filtration and crystallized from the proper solvent (Table I). The IR and ^{1}H-NMR were identical to that obtained from Method A.

Synthesis of Compound 5

A mixture of malononitrile (0.04 mol), carbon disulfide (0.04 mol), anhydrous potassium carbonate (3 gm), a catalytic amount of TBAB in dioxane (20 mL) was stirred for 40 minutes at 60°C. The dianionic ambident was added to compound **1** (0.04 mol). The reaction mixture was stirred for 6 h at 40°C and filtered off, and the organic layer was evaporated in vacuo. The residual solid was washed with water, collected by filtration, and crystallized from the proper solvent (Table I). IR, $\nu_{max:}$ 3110(NH), 2220(CN), 1680(CO), 1600(C=N). ^{1}H-NMR (DMSO-d_6), δ: 2.4 (s, 3H, SCH_3), 9.0(s, 1H, NH).

Synthesis of Compound 6

To a solution of compound **1** (0.01 mol) in acetic anhydride (5 mL), triethyl orthoformate (1 mL) was added. The reaction mixture was heated

under reflux for 5 h. The solvent was evaporated in vacuo and the residual solid was washed with water and crystallized from the proper solvent (Table I). IR, $\nu_{max:}$ 1730 (CO), 1600 (C=N). ^{1}H-NMR (DMSO-d_6), δ: 1.0–1.4 (2t, 6H, 2$\underline{CH_3}$-CH_2), 2.4 (s, 3H, SCH_3), 3.6 (q, 2H, CH_2), 4.2–4.4(q, 2H, $\underline{CH_2}$-CH_3), 9.0(s, 1H, =CH).

Synthesis of Compound 7

To a mixture of compound **1** (0.02 mol) and chloroacetyl chloride (0.02 mol) in dioxane (30 mL), a few drops of TEA were added. The reaction mixture was stirred at r.t. for 1 h; the solid that separated was collected by filteration, washed with water, dried and crystallized from the proper solvent (Table I). IR, ν_{max}: 3320(NH), 1700(CO), 1680(CO), 1600(C=N). ^{1}H-NMR (DMSO-d_6), δ: 1.0–1.3(t, 3H, CH_3), 2.3(s, 3 H, SCH_3), 3.8 (s, 2H, CH_2),4.0–4.4(q, 2H, CH_2), 9.4 (s, 1H, NH).

Synthesis of Compound 8

To a solution of compound **1** (0.01 mol) in glacial acetic acid (10 mL), 2,5-dimethoxytetrahydrofuran (0.02 mol) was added. The reaction mixture was heated under reflux for 1 h and evaporated in vacuo and the residual solid was filtered off, washed with water, and crystallized from the proper solvent (Table I). IR, $\nu_{max:}$ 3045 (CH arom.), 1710(CO), 1600(C=N). ^{1}H-NMR (DMSO-d_6), δ: 1.0–1.3(t, 3H, $\underline{CH_3}$-CH_2), 2.3(s, 3H, SCH_3),4.2–4.4(q, 2H, $\underline{CH_2}$-CH_3) 7.7–8.0 (m, 4H, Ar-H.).

Synthesis of Compound 9

Compound **1** (0.01 mol) was dissolved in dry toluene (100 mL), and Lawesson's reagent (0.01 mol) was added. The reaction mixture was heated under reflux for 4 h and then filtered while still hot. The filtrate was evaporated to dryness under reduced pressure, and the residue was washed with aqueous sodium hydrogen carbonate (40 mL, 10%) and water (20 mL). The solid product was filtered off, dried, and crystallized from the proper solvent (Table I). IR, $\nu_{max:}$ 3390(NH), 3055(CH-arom), 1690 (CO), 1600 (C=N), 1045 (P=S). ^{1}H-NMR (DMSO-d_6), δ: 2.3 (s, 3H, SCH_3), 3.5(s, 3H, OCH_3), 7.0–7.9 (m, 4H, Ar-H.).

Synthesis of Compound 10

To a mixture of compound **1** (0.02 mol) and benzylidinemalononitrile (0.02 mol) in dioxane (20 mL), triethyl amine (a few drops) was added, and the reaction mixture was refluxed for 4 h. Then the mixture was

left to cool. The product was collected by filtration, washed with water, dried, and crystallized from the proper solvent (Table I). IR, $\nu_{max.}$ 3310 (NH), 3060(CH arom.), 2230(CN), 1700 (CO), 1600 (C=N). ^{1}H-NMR (DMSO-d_6), δ: 2.3 (s, 3H, SCH_3) 7.4–8.1(m, 5H, Ar-H), 10.1(s, 1H, NH).

Synthesis of Compound 11

To a solution of compound **1** (0.03 mol) in ethanol (50 mL), hydrazine hydrate (0.05 mol) was added. The reaction mixture was refluxed for 8 h. The reaction mixture was left to cool, and the solid separated was collected, washed with water, and crystallized from the proper solvent (Table I). IR, $\nu_{max.}$ 3210, 3100 (NH_2), 1680 (CO), 1600 (C=N). ^{1}H-NMR ($CDCl_3$), δ: 2.3 (s, 3H, SCH_3), 5.2–5.4(br, 2H, NH_2), 11.2 (s, 1H, NH).

Synthesis of Compound 12

To a solution of compound **6** (0.01 mol) in ethanol (30 mL), hydrazine hydrate (0.02 mol) was added. The reaction mixture was refluxed for 3 h. The solvent was evaporated in vacuo and the residual solid was crystallized from the proper solvent (Table I). IR, $\nu_{max.}$ 3200, 3120 (NH_2), 1680 (CO), 1600 (C=N). ^{1}H-NMR (DMSO-d_6), δ: 2.4(s, 3H, SCH_3), 5.5–5.8 (br, 2H, NH_2), 8.6(s, 1H, =CH).

Synthesis of Compound 13

To a solution of compound **7** (0.01 mol) in dioxane (20 mL), malononitrile (0.01 mol) and few drops of TEA were added. The reaction mixture was refluxed for 1 h. The solvent was evaporated in vacuo and the residual solid was filtered off, washed with water, and crystallized from the proper solvent (Table I). IR, $\nu_{max.}$ 3200 (NH), 2230(CN), 1700(CO), 1690 (CO), 1610(C=N). ^{1}H-NMR (DMSO-d_6), δ: 2.3 (s, 3H, SCH_3), 4.1 (s, 2H, CH_2), 8.0 (s, 1H, NH).

Synthesis of Compound 14

A mixture of a freshly prepared polyphosphoric acid (5 g) and compound **8** (0.01 mol) was heated under reflux for 1 h at 150°C. The reaction mixture was left to cool and then poured onto cold water saturated with sodium carbonate. The solid that separated was collected by filtration and crystallized from the proper solvent (Table I). IR, $\nu_{max.}$ 3025(CH_{arom}), 1695(CO), 1600(C=N). ^{1}H-NMR (DMSO-d_6), δ: 2.3 (s, 3H, SCH_3). 7.7–8.0 (m, 3H, Ar-H).

Synthesis of Compound 15

A mixture of compound **11** (0.01 mol), acetic acid (15 mL) and acetic anhydride (10 mL) was heated under reflux for 5 h. The solvent was evaporated in vacuo and the residual solid was collected, washed with water, and crystallized from the proper solvent (Table I). IR, $\nu_{max:}$ 3410–3130 (NH +NH_2), 1695 (CO acetyl), 1610(C=N). ^{1}H-NMR (DMSO-d_6), δ: 2.1(s, 6H, 2CH_3CO) −2.4(s, 3H, SCH_3), 6.0–6.2 (br, 2H, NH_2), 8.0 (s, 1H, NH).

Synthesis of Compound 16

A mixture of compound **11** (0.01 mol) and formic acid (30 mL) was heated under reflux for 5 h. The solvent was evaporated in vacuo, and the residual solid was collected, washed with water, and crystallized from the proper solvent (Table I). IR, $\nu_{max:}$ 3120 (NH), 1725(CO aldehyde), 1690(CO amide), 1580(C=N). ^{1}H-NMR (DMSO-d_6), δ: 2.3(s, 3H, SCH_3), 6.6(s, 1H, =CH), 9.1(s, 1H, CHO), 10.3 (s, 1H, NH).

Synthesis of Compound 17

A mixture of compound **11** (0.01 mol) and *p*-chloro benzaldehyde (0.01 mol) in absolute ethanol (30 mL) was heated under reflux for 3 h. The reaction mixture was then left to cool, and the precipitate that formed was collected by filtration and crystallized from the proper solvent (Table I). IR, $\nu_{max:}$ 3410–3140 (NH +NH_2), 1690 (CO), 1590(C=N). ^{1}H-NMR (DMSO-d_6), 2.3(s, 3H, SCH_3), 7.8–8.3 (m, 4H, Ar-H), 5.9–6.1 (br, 2H, NH_2) 10.1 (s, 1H, NH).

Synthesis of Compound 18

A mixture of compound **17** (0.01 mol) and triethyl orthoformate (10 mL) was heated under reflux for 5 h. The solvent was evaporated in vacuo and the residual solid was collected, washed with water, and crystallized from the proper solvent (Table I). IR, $\nu_{max:}$ 1700(CO), 1600(C=N). ^{1}H-NMR (DMSO-d_6), 2.3(s, 3H, SCH_3), 6.1 (s, 1H, =CH), 7.6–8.1 (m, 4H, Ar-H).

Synthesis of Compound 19

A mixture of compound **11** (0.01 mol), acetic anhydride (5 mL) and triethyl orthoformate (10 mL) was heated under reflux for 4 h. The solvent was evaporated in vacuo and the residual solid was collected,

washed with water, and crystallized from the proper solvent (Table I). IR, $\nu_{max:}$ 1695(CO), 1570(C=N). ^{1}H-NMR (DMSO-d_6), δ: 1.1–1.4 (t, 2H, $\underline{CH_3}$-CH_2 ester), 2.3(s, 3H, SCH_3), 3.7 (q, 2H, $\underline{CH_2}$-CH_3), 6.0 (s, 1H, =CH).

Synthesis of Compound 20

To a solution of compound **11** (0.01 mol) in ethanol (30 mL), carbon disulfide (0.05 mol) and ethanolic solution of potassium hydroxide (0.5 gm/5 mL) were added. The reaction mixture was refluxed until the evolution of H_2S ceased (12 h). The solvent was evaporated in vacuo, and the remaining product then was poured into an ice water (200 mL) and HCl (10 mL) mixture. The separated solid was collected by filtration, washed with water, dried, and crystallized from the proper solvent (Table I). IR, ν_{max}: 3340, 3265, 3220 (NH + NH_2), 1710(CO), 1600(C=N), 1140(C=S). ^{1}H-NMR (DMSO-d_6), δ: 2.3 (s, 3H, SCH_3), 5.1–5.3 (br, 2H, NH_2), 10.2(s, 1H, NH).

Synthesis of Compound 21

A mixture of compound **11** (0.02 mol) and 2-(bis-methylsulfanyl-methylene)-malononitrile (0.02 mol) was dissolved in ter. butanol (30 ml) containing few drops of triethyl amine and was heated under reflux for 12 h until the evolution of MeSH ceased. The solvent was evaporated in vacuo, and the remaining product was triturated with pet. ether (40–60°C), and the residual solid was collected by filtration and crystallized from the proper solvent (Table I). IR, ν_{max}: 3345, 3265, 3200, 3175 (2 NH_2), 2200 (CN), 1695 (CO), 1610(C=N), 670 (P=S). ^{1}H-NMR (DMSO -d_6), δ: 2.3, 2.5 (2s, 6 H, 2 SCH_3) 4.7–4.9 (br, 2H, NH_2), 6.0–6.3 (br, 2H, NH_2).

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