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Synthesis and Reactions of 5-Amino-3-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-7-phenyl-7*H*-thiazolo[3,2-*a*]pyrimidine-6-carbonitrile

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Summary. 5-Amino-3-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-7-phenyl-7*H*-thiazolo[3,2-*a*]pyrimidine-6-carbonitrile was synthesized *via* the reaction of 4-(2-aminothiazol-4-yl)-3-methyl-1-phenyl-2-pyrazolin-5-one with benzylidene malononitrile and was then transformed to related fused heterocyclic systems. The antifungal and antibacterial studies revealed in some cases excellent biocidal properties.

Keywords. Heterocycles; Pyrazolone; Thiazole; Thiazolopyrimidine; Pyrimidothiazolopyrimidine.

Introduction

5-Pyrazolone is widely used as precursor for the synthesis of different heterocycles with biological and medicinal activities [1–5]. Heterocycles containing a thiazole ring are associated with a particularly wide range of biological properties including antiprotozoal [6] and anticonvulsants [7] activity as well as a depressant effect on the central nervous system [8], as antihelminthics [9], antidiabetics [10], and inhibitors of dihydrofolate [11]. In the present study we report herein a simple synthesis method for the preparation of 5-amino-3-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-7-phenyl-7*H*-thiazolo[3,2-*a*]pyrimidine-6-carbonitrile (**2**) and its transformation to related fused heterocyclic systems.

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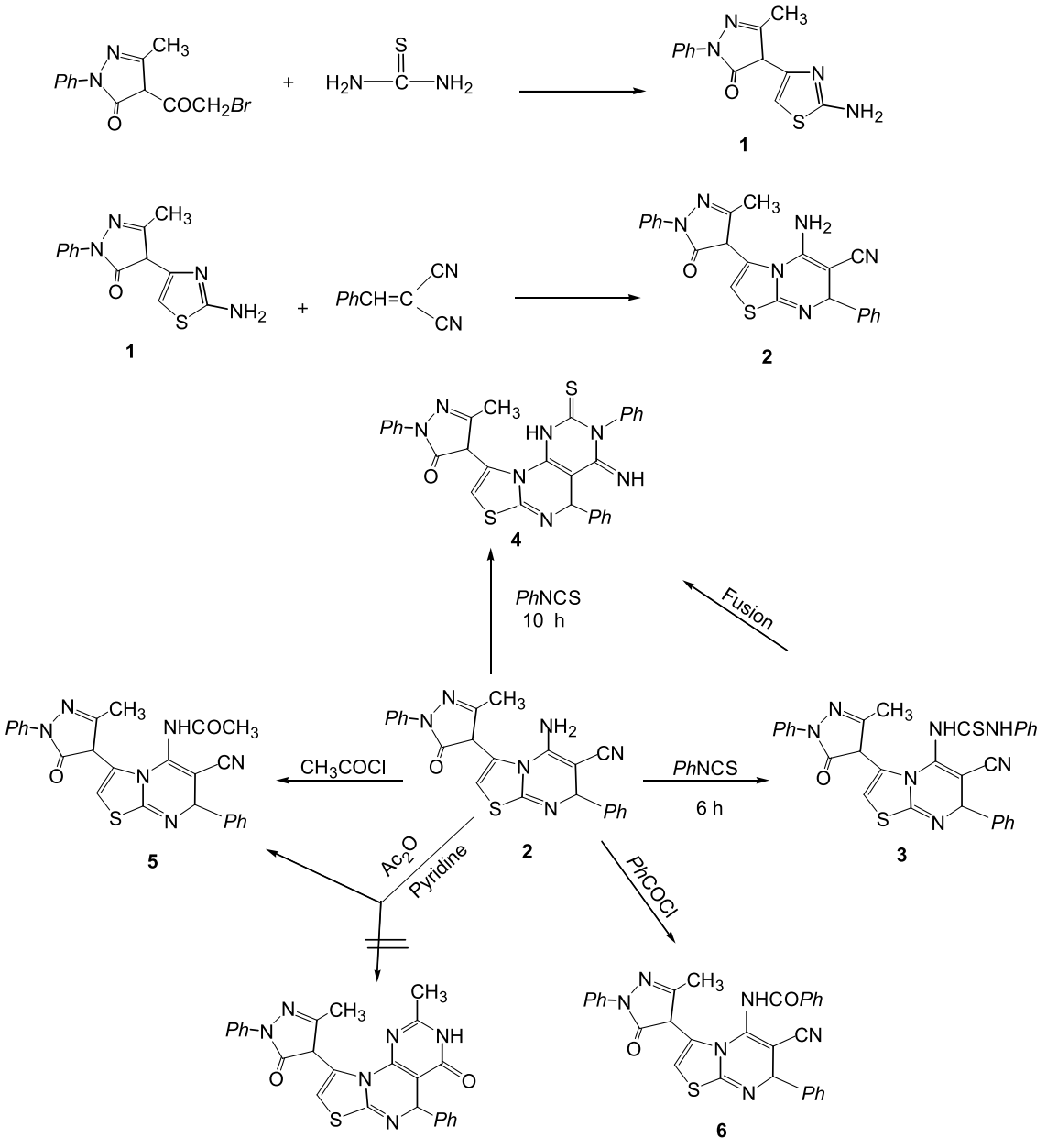
Results and Discussion

Syntheses

Compound **1** was prepared by reaction of 4-bromoacetyl-3-methyl-1-phenyl-2-pyrazolin-5-one with thiourea. Then **1** was used as a candidate for the synthesis of 5-amino-3-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-7-phenyl-7*H*-thiazolo[3,2-*a*]pyrimidine-6-carbonitrile (**2**) and its fused derivatives. For this purpose the target compound **2** was prepared by interaction of **1** with benzylidenemalononitrile. The reaction of **2** with phenyl isothiocyanate in pyridine for 6 h provided 3-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-5-(*N*-phenylthiourea)-7-phenyl-7*H*-thiazolo[3,2-*a*]pyrimidine-6-carbonitrile (**3**), but when the reaction mixture was refluxed for 10 h it gave 3,5-diphenyl-9-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-1,5-dihydro-4-imino-2-thioxo-2*H*-pyrimido[5,4-*e*]thiazolo[3,2-*a*]pyrimidine (**4**), the latter compound could be also obtained by fusion of **3** over its melting point.

Whereas the reaction of **2** with acetyl chloride in the presence of pyridine as catalyst produced 5-acetylamino-3-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-7-phenyl-7*H*-thiazolo[3,2-*a*]pyramidine-6-carbonitrile (**5**), the acetylamino derivative was also produced by the reaction of **2** with acetic anhydride/pyridine (2/1 *v*/*v*) instead of 2-methyl-9-(3-methyl-1-phenyl-2-pyrazolin-4-yl)-3,5-dihydro-

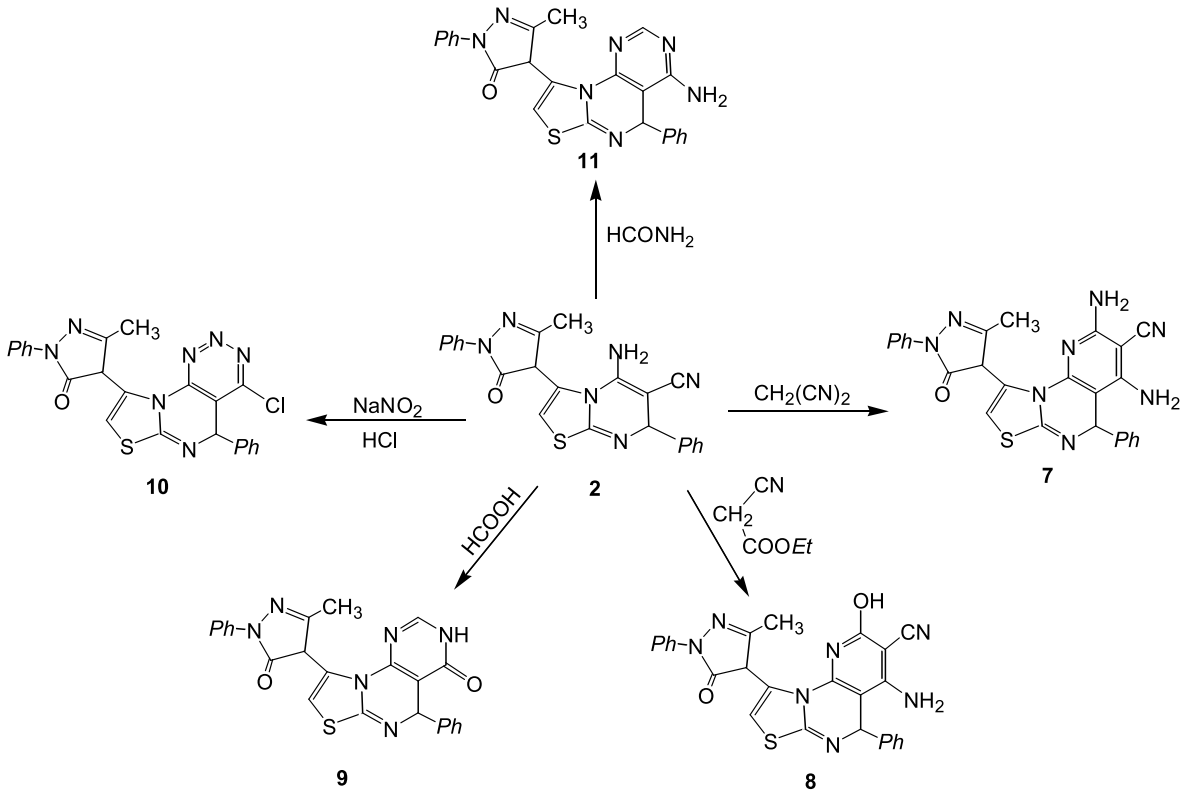


Scheme 1

5-phenyl-4*H*-pyrimido[5,4-*e*]thiazolo[3,2-*a*]pyrimidin-4-one. Also, the reaction of **2** with benzoyl chloride gave 5-benzoylamino-3-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-7-phenyl-7*H*-thiazolo[3,2-*a*]-pyrimidine-6-carbonitrile (**6**).

Treatment of **2** with malononitrile or ethyl cyanoacetate gave 2,4-diamino-9-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-5-phenyl-5*H*-pyrimido-[3,2-*e*]thiazolo[3,2-*a*]pyrimidine-3-carbonitrile (**7**) or 4-amino-9-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-2-hydroxy-5-phenyl-5*H*-pyrido[3,2-*e*]thiazolo-[3,2-*a*]pyrimidine-3-carbonitrile (**8**).

Refluxing **2** with formic acid gave 9-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-3,5-dihydro-5-phenyl-4*H*-pyrimido[5,4-*e*]thiazolo[3,2-*a*]pyrimidin-4-one (**9**). Reaction of nitrous acid with **2** under ordinary conditions afforded 4-chloro-9-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-5-phenyl-5*H*-thiazolo[2′,3′:2,3]pyrimido[4,5-*d*][1,2,3]triazine (**10**) while the reaction of **2** with formamide provided 4-amino-9-



Scheme 2

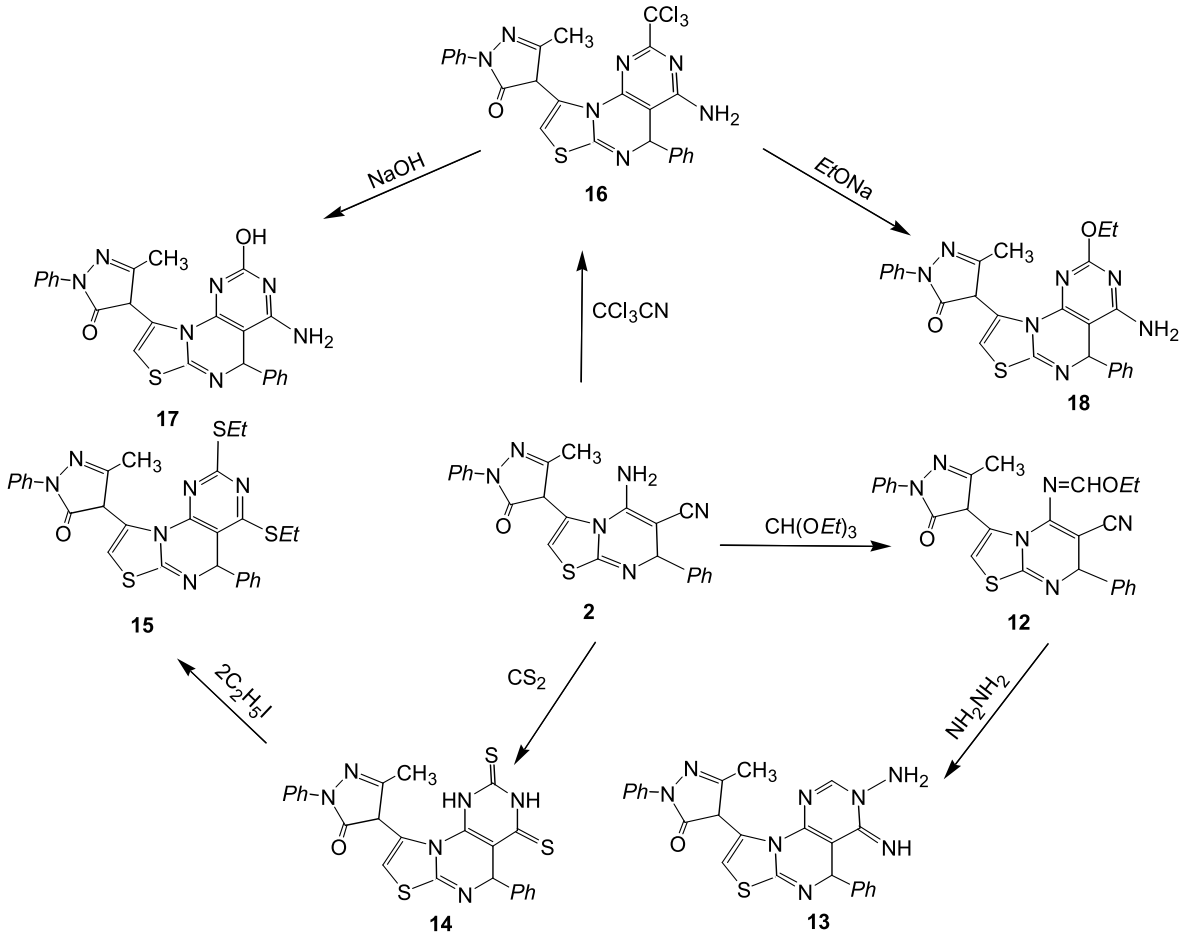
(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-5-phenyl-5*H*-pyrimido[5,4-*e*]thiazolo[3,2-*a*]pyrimidine (**11**).

The reaction of **2** with excess of triethyl orthoformate led to the formation of 5-(ethoxymethyleneamino)-3-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-7-phenyl-7*H*-thiazolo[3,2-*a*]pyrimidine-6-carbonitrile (**12**). Attempts to cyclize **12** by stirring in absolute ethanol containing an excess hydrazine hydrate afforded 3-amino-9-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-3,5-dihydro-4-imino-5-phenyl-4*H*-pyrimido[5,4-*e*]thiazolo[3,2-*a*]pyrimidine (**13**). Carbon disulfide reacted with **2** in pyridine to give 9-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-5-phenyl-2, 4-dithioxo-1, 3, 4, 5-tetrahydro-2*H*-pyrimido[5,4-*e*]thiazolo[3,2-*a*]pyrimidine (**14**), which on subsequent alkylation with ethyl iodide afforded 2,4-bis(ethylthio)-9-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-5-phenyl-5*H*-pyrimido[5,4-*e*]thiazolo-[3,2-*a*]pyrimidine (**15**). Also, on refluxing **2** with trichloroacetonitrile in toluene in presence of a catalytic amount of piperidine yields 4-amino-9-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-2-trichloromethyl-5-phenyl-5*H*-pyrimido[5,4-*e*]thiazolo[3,2-*a*]-pyrimidine (**16**), the trichloro moiety in **16** could be substituted by a hydroxyl group on refluxing with aqueous sodium hydroxide solution, and by an ethoxy group on boiling with sodium ethoxide in ethanol to give 4-amino-2-hydroxy-9-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-5-phenyl-5*H*-pyrimido[5,4-*e*]thiazolo [3,2-*a*]-pyrimidine (**17**) and 4-amino-2-ethoxy-9-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-5-phenyl-5*H*-pyrimido[5,4-*e*]thiazolo-[3,2-*a*]pyrimidine (**18**).

The structure of new compounds was confirmed on the basis of elemental analyses as well as spectral data (IR, ^{1}H NMR, and MS).

Biological Activity

Some of the prepared compounds were tested for their antimicrobial activity against six fungal and five bacterial species (Table 1). Compounds **15** and **17** showed a wide spectrum of antifungal action but a narrow spectrum of antibacterial effect with minimum inhibitory concentrations (*MIC*) ranging from 5–50 mg/cm^3 (Table 1). Compound **13** was only effective against three fungal species including *Aspergillus flavus*, *Aspergillus niger*, and *Trichophyton*



Scheme 3

Table 1. The minimum inhibitory concentrations of the compounds tested (mg/cm^3)

Organisms	Compounds										
	2	**3**	**4**	**7**	**8**	**11**	**12**	**13**	**15**	**17**	Ref.*
Fungi											
Aspergillus flavus	–	–	–	–	–	–	–	20	20	–	10
Aspergillus niger	–	–	–	–	–	–	–	20	20	50 (p.i.)	10
Candida albicans	20	–	–	–	–	–	–	–	20	50	10
Geotrichum candidum	20	–	50	50 (p.i.)	10	10	10	–	10	20	10
Scopulariopsis brevicaulis	–	–	–	–	–	–	–	–	–	50	10
Trichophyton rubrum	–	–	50	–	–	–	–	20	20	50	10
Bacteria											
Bacillus cereus (*Gram* positive)	20	50	50	–	–	–	2	–	2	10	10
Staphylococcus aureus (*Gram* positive)	20	–	–	–	50	–	5	–	5	10	10
Pseudomonas aeruginosa (*Gram* negative)	–	–	–	–	–	–	–	–	–	5	10
Serratia marcescens (*Gram* negative)	20	–	–	50	–	–	–	–	–	–	10
Escherichia coli (*Gram* negative)	–	–	–	–	–	50	–	–	–	–	10

* *Ref.* Reference drugs = chloramphenicol as antibacterial and clotrimazole as antifungal
– No antimicrobial action
p.i. Partial inhibition

rubrum. The remaining compounds exhibited a narrow spectrum of antimicrobial action. Their inhibitory effect was often confined to the fungus *Geotrichum candidum*, and *Gram* positive bacteria *Bacillus cereus* and *Staphylococcus aureus* with *MIC* ranging from 2 to 50 mg/cm^3. It is to be mentioned that *Gram* negative bacteria *Escherichia coli*, *Pseudomonas aeruginosa*, and *Serratia marcescens* were generally resistant to the compounds tested. Exceptions were observed with *P. aeruginosa*, which was inhibited by **17** (*MIC* 5 mg/cm^3). *S. marcescens* was suppressed by compounds **2** and **7** which were effective at concentrations ranging from 20 to 50 mg/cm^3. Among the tested fungi *G. candidum* was the most sensitive organism to the compounds tested. As shown in Table 1, *Candida albicans* and *T. rubrum* were only sensitive to four out of the ten compounds. *A. niger* was inhibited by three compounds. *A. flavus* and *S. brevicaulisulis* showed sensitivity towards two of the compounds tested. Comparing the *MIC* of the effective compounds with those of the reference drugs (chlotrimazole as antifungal and chloramphenicol as antibacterial) revealed that compound **12** was effective against *Gram* positive bacteria at concentrations ranging from 2 to 5 mg/cm^3 which are comparatively lower than the *MIC* of chloramphenicol (10 mg/cm^3), also compound **17** was effective against *P. aeruginosa* at 5 mg/cm^3. Otherwise the *MIC* of the antimicrobial compounds were equal or higher than those of the reference drugs.

Experimental

Melting points were determined on APP. Digital ST 15 melting point apparatus. Elemental analyses (C, H, N, and S) were conducted using a Vario EL C, H, N, and S Analyzer; their results were found to be in good agreement (±0.3%) with the calculated values. The IR spectra were obtained on a Pye-Unicam SP 3-100 spectrophotometer using the KBr disc technique ($\bar{\nu}_{max}$ in cm^{-1}). ^{1}H NMR spectra were recorded on JNMFT 400 Lambda series and EM 390 NMR spectrometer, chemical shifts were given in ppm in a suitable deuterated solvent using *TMS* as an internal standard and the mass spectra were run on JOEL JMS 600 spectrometer.

4-(2-Aminothiazol-4-yl)-3-methyl-1-phenyl-2-pyrazolin-5-one (**1**, $C_{13}H_{12}N_4OS$)

A mixture of 6.00 g 4-bromoacetyl-3-methyl-1-phenyl-2-pyrazolin-5-one (20 mmol) and 1.52 g thiourea (20 mmol) in 100 cm^3 absolute ethanol was refluxed for 5 h. The reaction mixture was concentrated, cooled, and neutralized with sodium acetate solution (6%). The precipitated solid was filtered off, washed with water, dried, and crystallized from benzene to give 4.10 g (75%) **1**. Mp 234°C; ^{1}H NMR (90 MHz, *DMSO*-d_6): $\delta = 2.90$ (s, CH_3), 5.01 (s, NH_2), 7.11 (s, thiazole-H), 7.41–8.10 (m, Ar–H, pyrazole-H) ppm; IR (KBr): $\bar{\nu} = 3300$, 3400 (NH_2), 3100 (CH aliphatic), 1705 (C=O) cm^{-1}; MS (70 ev): m/z (%) = 271.78 (M^+, 100).

5-Amino-3-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-7-phenyl-7H-thiazolo[3,2-a]pyramidine-6-carbonitrile (**2**, $C_{23}H_{18}N_6OS$)

A mixture of 3.30 g **1** (12 mmol) and 1.80 g benzylidene malononitrile (12 mmol) in 50 cm^3 absolute ethanol containing 0.5 cm^3 triethylamine was refluxed for 7 h, then cooled and poured into cold water, and the solid thus formed was filtered off, washed several times with water, and recrystallized from benzene to give 3.70 g (73%) **2**. Mp 225°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.21$ (s, CH_3), 4.50 (s, NH_2), 7.09 (s, thiazole-H), 6.11 (s, pyrimidine-H), 7.30 (s, pyrazole-H), 7.40–8.20 (m, Ar–H) ppm; IR (KBr): $\bar{\nu} = 3215$, 3425 (NH_2), 2175 (CN), 1705 (C=O) cm^{-1}; MS (70 ev): m/z (%) = 425.69 (M^+, 72.4).

3-(3-Methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-5(N-phenylthiourea)-7-phenyl-7H-thiazolo[3,2-a]pyrimidine-6-carbonitrile (**3**, $C_{30}H_{23}N_7OS_2$)

A mixture of 1.23 g **2** (2.8 mmol) and 0.36 cm^3 phenyl isothiocyanate (2.8 mmol) in 20 cm^3 pyridine was refluxed for 6 h, poured into ice water, filtered off, dried, and recrystallized from ethanol to afford 0.96 g (75%) **3**. Mp 215°C; ^{1}H NMR (90 MHz, *DMSO*-d_6): $\delta = 2.21$ (s, CH_3), 6.11 (s, pyrimidine-H), 7.11 (s, thiazole-H), 7.21–8.20 (m, Ar–H, pyrazole-H), 9.20 (s, NH), 10.31 (s, NH) ppm; IR (KBr): $\bar{\nu} = 3400$ (NH), 2200 (CN), 1705 (C=O), 1500 (C=S) cm^{-1}.

3,5-Diphenyl-9-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-1,5-dihydro-4-imino-2-thioxo-2H-pyrimido[5,4-e]thiazolo-[3,2-a]pyrimidine (**4**, $C_{30}H_{23}N_7OS_2$)

A mixture of 1.23 g **2** (2.8 mmol) and 0.36 cm^3 phenyl isothiocyanate (2.8 mmol) in 20 cm^3 pyridine was refluxed for 10 h, poured into ice water, filtered off, dried, and recrystallized from ethanol to give 0.93 g (73%) **4**. Mp 260°C; ^{1}H NMR (90 MHz, $CDCl_3$): $\delta = 2.20$ (s, CH_3), 4.30 (s, imino-H), 6.10 (s, pyrimidine-H), 7.11 (s, thiazole-H), 9.91 (s, NH), 7.31–7.81 (m, Ar–H, pyrazole-H) ppm; IR (KBr): $\bar{\nu} = 3400$ (NH), 1705 (C=O), 1600 (C=N), 1505 (C=S) cm^{-1}, disappearance of CN group.

*An Alternative Route for the Preparation of **4***

One gram of **3** was fused over its melting point (225°C) for 2 h, then cooled; and the solid product thus formed was recrystallized from ethanol to give dark red powder of **4**. It was found that the compound **4** was identical with that prepared above.

5-Acetylamino-3-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-7-phenyl-7H-thiazolo[3,2-a]pyrimidine-6-carbonitrile (**5**, $C_{25}H_{20}N_6O_2S$)

A mixture of 1.00 g **2** (2.3 mmol) and 5 cm^3 acetyl chloride in 10 cm^3 pyridine was refluxed for 3 h. The reaction

mixture was cooled and poured into cold water, then the solid product was filtered off and recrystallized from benzene to give 0.87 g (81%) **5**. Mp 245°C; ^{1}H NMR (90 MHz, $CDCl_3$): $\delta = 2.21$ (s, CH_3), 2.41 (s, CH_3 of acetyl), 6.10 (s, pyrimidine-H), 7.11 (s, thiazole-H), 7.30–8.62 (m, Ar–H, pyrazole-H), 10.31 (s, NH) ppm; IR (KBr): $\bar{\nu} = 3200$ (NH), 2200 (CN), 1705 (C=O), 1680 (C=O of acetamide) cm^{-1}.

An Alternative Route for the Preparation of ***5***

A mixture of 1.23 g **2** (2.8 mmol) in 30 cm^3 acetic anhydride/pyridine mixture (2/1 *v*/*v*) was heated under reflux for 4 h. The reaction mixture was cooled and poured into cold water, then the solid product was filtered off and recrystallized from ethanol to give yellow crystals of **5**. It was found that the compound **5** was identical in all aspects (mp, mixed mp, IR, and ^{1}H NMR) with that prepared from **2** with acetyl chloride.

5-Benzoylamino-3-(-3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-7-phenyl-7H-thiazolo[3,2-a]pyrimidine-6-carbonitrile (**6**, $C_{30}H_{22}N_6O_2S$)

A mixture of 1.00 g **2** (2.3 mmol) and 5 cm^3 benzoyl chloride in 10 cm^3 pyridine was refluxed for 3 h. The reaction mixture was cooled and treated with 50 cm^3 petroleum ether (60–80°C) whereby solid product was separated, collected by filtration, and recrystallized from ethanol to give 0.93 g (75%) **6**. Mp 250°C; ^{1}H NMR (90 MHz, $CDCl_3$): $\delta = 2.20$ (s, CH_3), 6.10 (s, pyrimidine-H), 7.10 (s, thiazole-H), 7.30–7.80 (m, Ar–H, pyrazole-H), 10.20 (s, NH) ppm; IR (KBr): $\bar{\nu} = 3300$ (NH), 2200 (CN), 1710 (C=O), 1630 (C=O of benzamide) cm^{-1}.

2,4-Diamino-9-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-5-phenyl-5H-pyrido[3,2-e]thiazolo[3,2-a]pyrimidine-3-carbonitrile (**7**, $C_{26}H_{20}N_8OS$)

A mixture of 1.00 g **2** (2.3 mmol) and 0.15 g malononitrile (2.3 mmol) in 20 cm^3 pyridine was refluxed for 4 h. The reaction mixture was cooled and poured into cold water whereby solid product was separated, filtered off, and recrystallized from benzene to afford 0.77 g (67%) **7**. Mp 300°C; ^{1}H NMR (90 MHz, *DMSO*-d_6): $\delta = 2.20$ (s, CH_3), 4.90 (s, $2NH_2$), 6.10 (s, pyrimidine-H), 7.10 (s, thiazole-H), 7.30–7.80 (m, Ar–H, pyrazole-H) ppm; IR (KBr): $\bar{\nu} = 3300$, 3400 (NH_2), 2200 (CN), 1710 (C=O) cm^{-1}.

4-Amino-2-hydroxy-9-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-5-phenyl-5H-pyrido[3,2-e]thiazolo[3,2-a]pyrimidine-3-carbonitrile (**8**, $C_{26}H_{19}N_7O_2S$)

A mixture of 1.00 g **2** (2.3 mmol) and 0.26 cm^3 ethyl cyanoacetate (2.3 mmol) in 20 cm^3 pyridine was refluxed for 4 h. The reaction mixture was cooled and poured into cold water whereby solid product was separated, filtered off, and recrystallized from benzene to give 0.75 g (65%) **8**. Mp 310°C; ^{1}H NMR (90 MHz, *DMSO*-d_6): $\delta = 2.20$ (s, CH_3), 4.90 (s, NH_2), 6.10 (s, pyrimidine-H), 7.10 (s, thiazole-H), 7.30–7.80 (m, Ar–H, pyrazole-H), 9.50 (s, OH) ppm; IR (KBr): $\bar{\nu} = 3300$, 3400 (NH_2), 2200 (CN), 1710 (C=O) cm^{-1}.

9-(3-Methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-3,5-dihydro-5-phenyl-4H-pyrimido[5,4-e]thiazolo[3,2-a]pyrimidin-4-one (**9**, $C_{24}H_{18}N_6O_2S$)

A mixture of 1.23 g **2** (2.8 mmol) and 3 cm^3 formic acid (6.5 mmol) was refluxed for 5 h. The reaction mixture was poured into cold water whereby the product thus formed was separated, filtered off, dried, and recrystallized from toluene to afford 1.04 g (80%) **9**. Mp 260°C; ^{1}H NMR (90 MHz, *DMSO*-d_6): $\delta = 2.30$ (s, CH_3), 6.10 (s, pyrimidine-H), 7.10 (s, thiazole-H), 7.30–7.70 (m, Ar–H, pyrazole-H), 10.30 (s, NH) ppm; IR (KBr): $\bar{\nu} = 3300$ (NH), 1705 (C=O), 1640 (C=O of pyrimidine) cm^{-1}; MS (70 ev): m/z (%) = 454.38 (M^+, 72.4).

4-Chloro-9-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-5-phenyl-5H-thiazolo[2′,3′:2,3]pyrimido[4,5-d][1,2,3]triazine (**10**, $C_{23}H_{16}N_7OSCl$)

To a mixture of 1.23 g **2** (2.8 mmol) and 3 cm^3 hydrochloric acid, a solution of 0.016 g sodium nitrite (2.8 mmol) in 5 cm^3 cold water was added with stirring at 5°C. After complete addition of sodium nitrite solution, the product was precipitated, then collected by filtration, and crystallized from ethanol to give 0.94 g (70%) **10**. Mp 280°C; ^{1}H NMR (90 MHz, *DMSO*-d_6): $\delta = 2.20$ (s, CH_3), 6.10 (s, pyrimidine-H), 7.10 (s, thiazole-H), 7.31–7.70 (m, Ar–H, pyrazole-H) ppm; IR (KBr): $\bar{\nu} = 1705$ (C=O) cm^{-1}, disappearance of CN and NH_2 groups.

4-Amino-9-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-5-phenyl-5H-pyrimido[5,4-e]thiazolo[3,2-a]pyrimidine (**11**, $C_{24}H_{19}N_7OS$)

A mixture of 1.23 g **2** (2.8 mmol) and 3 cm^3 formamide was refluxed for 4 h, then cooled and poured into ice-water mixture. The precipitate thus formed was collected by filtration, washed several times with water, and crystallized from benzene to give 0.74 g (70%) **11**. Mp 217°C; ^{1}H NMR (90 MHz, $CDCl_3$): $\delta = 2.40$ (s, CH_3), 4.30 (s, NH_2), 6.10 (s, pyrimidine-H), 7.10 (s, thiazole-H), 7.40–7.70 (m, Ar–H, pyrazole-H) ppm; IR (KBr): $\bar{\nu} = 3215$–3420 (NH_2), 1705 (C=O) cm^{-1}, disappearance of CN group; MS (70 ev): m/z (%) = 454.09 (M^+, 82.4).

5-(Ethoxymethyleneamino)-3-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-7-phenyl-7H-thiazolo[3,2-a]pyrimidine-6-carbonitrile (**12**, $C_{26}H_{22}N_6O_2S$)

A mixture of 1.23 g **2** (2.8 mmol) and 5 cm^3 triethyl orthoformate (30 mmol) was heated under reflux for 7 h. After cooling the reaction mixture was poured into cold water and the solid product thus formed was filtered off, dried, and recrystallized from benzene to afford 1.00 g (74%) **12**. Mp 263°C; ^{1}H NMR (90 MHz, *DMSO*-d_6): $\delta = 1.20$ (t, CH_3), 1.90 (q, CH_2), 2.20 (s, CH_3 of pyrazole), 4.10 (s, CH=N), 6.10 (s, pyrimidine-H), 7.10 (s, thiazole-H), 7.30–7.80 (m, Ar–H, pyrazole-H) ppm; IR (KBr): $\bar{\nu} = 2200$ (CN), 1705 (C=O), 1590 (C=N) cm^{-1}; MS (70 ev): m/z (%) = 481.19 (M^+, 25.4).

3-Amino-9-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-3,5-dihydro-4-imino-5-phenyl-4H-pyrimido[5,4-e]thiazolo-[3,2-a]pyrimidine (**13**, $C_{24}H_{20}N_8OS$)
A mixture of 0.70 g **12** (1.4 mmol) and 2 cm^3 hydrazine hydrate (40 mmol) in absolute ethanol was stirred at rt for 24 h. The precipitated product was collected by filtration and recrystallized from absolute ethanol to give 0.53 g (78%) **13**. Mp 285°C; ^{1}H NMR (90 MHz, *DMSO*-d_6): $\delta = 2.20$ (s, CH_3), 4.30 (s, imino-H), 4.80 (s, NH_2), 6.10 (s, pyrimidine-H), 7.10 (s, thiazole-H), 7.80–7.90 (m, Ar–H, pyrazole-H) ppm; IR (KBr): $\bar{\nu} = 3400$ (NH_2), 3500 (NH), 1705 (C=O), 1595 (C=S) cm^{-1}, disappearance of CN group; MS (70 ev): m/z (%) = 467.95 (M^+, 65.4).

9-(3-Methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-5-phenyl-2,4-dithioxo-1,3,4,5-tetrahydro-2H-pyrimido[5,4-e]thiazolo-[3,2-a]pyrimidine (**14**, $C_{24}H_{18}N_6OS_3$)
A mixture of 4.26 g **2** (10 mmol) and 5 cm^3 carbon disulfide (10 mmol) was heated on a water bath for 8 h. The reaction mixture was poured into cold water and the solid product thus formed was filtered off, dried, and recrystallized from benzene to give 3.5 g (70%) **14**. Mp 250°C; ^{1}H NMR (400 MHz, *DMSO*-d_6): $\delta = 2.40$ (s, CH_3), 6.10 (s, pyrimidine-H), 7.10 (s, thiazole-H), 7.11–7.40 (m, Ar–H, pyrazole-H), 7.90 (s, 2NH) ppm; IR (KBr): $\bar{\nu} = 3200$ (NH), 1710 (C=O), 1540–1570 (C=S) cm^{-1}; MS (70 ev): m/z (%) = 501.09 (M^+, 82.4).

2,4-Bis(ethylthio)-9-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-5-phenyl-5H-pyrimido[5,4-e]thiazolo[3,2-a]pyrimidine (**15**, $C_{28}H_{26}N_6OS_3$)
A mixture of 0.50 g **14** (9.9 mmol) and 1.00 cm^3 ethyl iodide (9.9 mmol) in 20 cm^3 absolute ethanol in the presence of 1.50 g anhydrous sodium acetate was refluxed for 3 h. The solid product thus precipitated was collected by filtration and recrystallized from ethanol to give 0.38 g (70%) **15**. Mp 235°C; ^{1}H NMR (90 MHz, *DMSO*-d_6): $\delta = 1.30$ (t, $2CH_3$), 2.20 (s, CH_3), 4.20 (q, $2CH_2$), 6.10 (s, pyrimidine-H), 7.20 (s, thiazole-H), 7.30–8.10 (m, Ar–H, pyrazole-H) ppm; IR (KBr): $\bar{\nu} = 2950$ (CH aliphatic), 1705 (C=O) cm^{-1}.

4-Amino-9-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-2-trichloromethyl-5-phenyl-5H-pyrimido[5,4-e]thiazolo[3,2-a]-pyrimidine (**16**, $C_{25}H_{18}N_7OSCl_3$)
A mixture of 4.26 g **2** (10 mmol) and 1.00 cm^3 trichloroacetonitrile (10 mmol) was refluxed in 25 cm^3 dry toluene containing a catalytic amount of piperidine for 3 h. The product which was separated during the reflux was filtered off, dried, and recrystallized from dioxane to give 4.35 g (76%) **16**. Mp 300°C; ^{1}H NMR (90 MHz, *DMSO*-d_6):$\delta = 2.40$ (s, CH_3), 4.90 (s, NH_2), 6.10 (s, pyrimidine-H), 7.10 (s, thiazole-H), 7.40–7.90 (m, Ar–H, pyrazole-H) ppm; IR (KBr): $\bar{\nu} = 3100$, 3200 (NH_2), 1705 (C=O) cm^{-1}, disappearance of CN group.

4-Amino-2-hydroxy-9-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-5-phenyl-5H-pyrimido[5,4-e]thiazolo[3,2-a]-pyrimidine (**17**, $C_{24}H_{19}N_7O_2S$)
A mixture of 0.50 g **16** (0.87 mmol) and solution of 0.50 g sodium hydroxide in 5 cm^3 H_2O was refluxed for 0.5 h. The product obtained was collected by filtration and recrystallized from ethanol to give 0.29 g (72%) **17**. Mp 293°C; ^{1}H NMR (90 MHz, *DMSO*-d_6): $\delta = 2.20$ (s, CH_3), 4.92 (s, NH_2), 6.10 (s, pyrimidine-H), 7.10 (s, thiazole-H), 7.40–7.70 (m, Ar–H, pyrazole-H) ppm; IR (KBr): $\bar{\nu} = 3300$ (NH_2), 3400 (OH), 1710 (C=O) cm^{-1}.

4-Amino-2-ethoxy-9-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-5-phenyl-5H-pyrimido[5,4-e]thiazolo[3,2-a]-pyrimidine (**18**, $C_{26}H_{23}N_7O_2S$)
A mixture of 0.50 g **16** (0.87 mmol) and sodium ethoxide (0.1 g Na/10 cm^3 absolute ethanol) was refluxed for 0.5 h. After cooling, the precipitated solid was collected by filtration and recrystallized from dioxane to give 0.30 g (69%) **18**. Mp 290°C; ^{1}H NMR (90 MHz, *DMSO*-d_6): $\delta = 1.30$ (t, CH_3), 2.40 (s, CH_3), 3.10 (q, CH_2), 4.90 (s, NH_2), 6.10 (s, pyrimidine-H), 7.10 (s, thiazole-H), 7.40–7.90 (m, Ar–H, pyrazole-H) ppm; IR (KBr): $\bar{\nu} = 3200$ (NH_2), 1705 (C=O) cm^{-1}.

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