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Reactions of 4-(2-aminothiazole-4-yl)-3-methyl-5-oxo-1-phenyl-2-pyrazoline. Synthesis of thiazolo[3,2-*a*]pyrimidine and imidazo[2,1-*b*]thiazole derivatives

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Abstract 4-(2-Aminothiazol-4-yl)-3-methyl-5-oxo-1-phenyl-2-pyrazoline was synthesized *via* the reaction of 4-bromoacetyl-3-methyl-5-oxo-1-phenyl-2-pyrazoline with thiourea [7] and was transformed to related fused heterocyclic systems. The antifungal and antibacterial studies revealed in some cases excellent biocidal properties.

Keywords Heterocycles; Pyrazolone; Thiazole; Thiazolopyrimidine; Imidazothiazole.

Introduction

The thiazole ring unit is a common structural feature in various bioactive molecules [1]. This heterocyclic system has been employed in the preparation of different important drugs required for treatment of inflammations [2], bacterial infections [3], and hypertension [4]. Some of the thiazole analogues are used as fungicides, inhibiting *in vivo* the growth of xanthomonas and as ingredients of herbicides, antischistosomicidal, and anthelmintic drugs [5]. Aminothiazoles are known to be ligands of the estrogen receptor and as a novel class of adenosine receptor antagonists [6]. Recently, we have developed reactions of aminothiazole and synthesis of thiazolo[3,2-*a*]pyrimidine and imidazo[2,1-*b*]thiazole derivatives.

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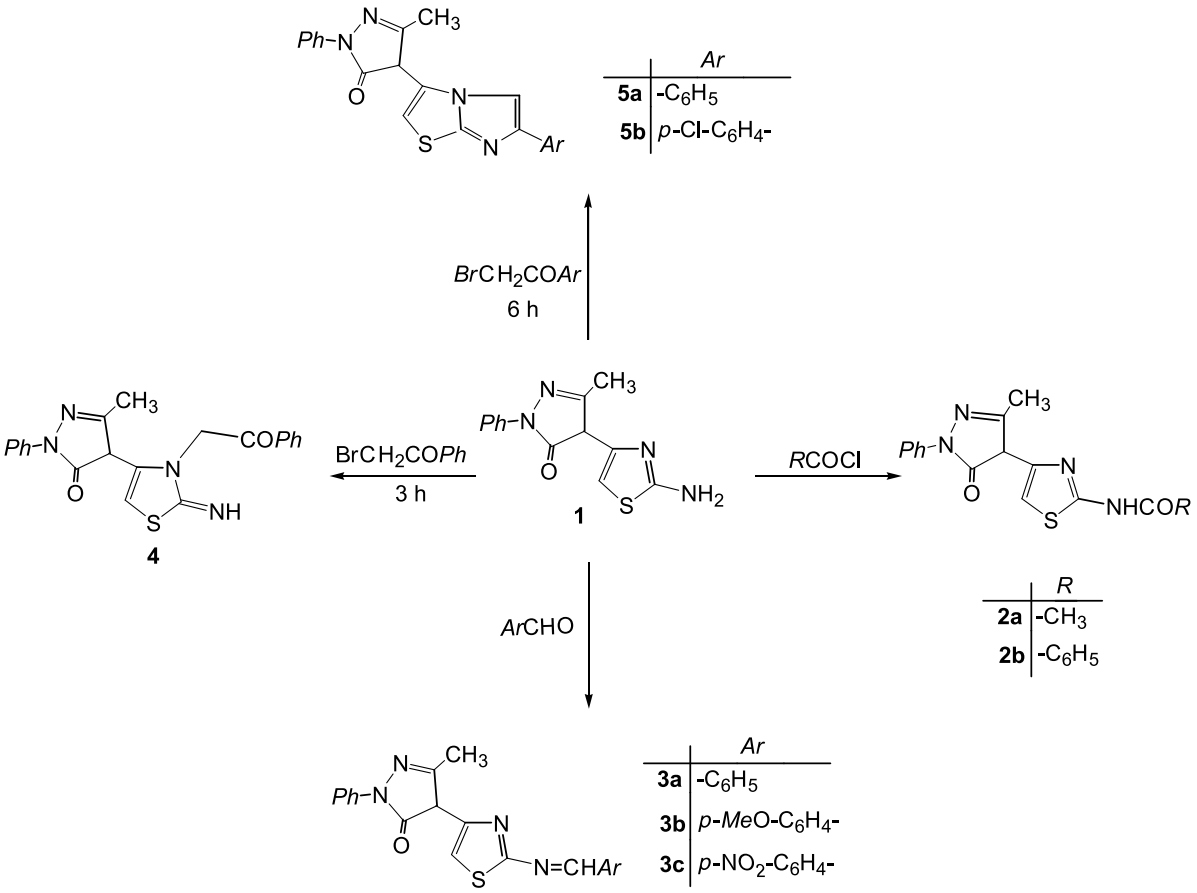
Results and discussion

Syntheses

The starting compound 4-(2-aminothiazol-4-yl)-3-methyl-5-oxo-1-phenyl-2-pyrazoline (**1**) [7] was refluxed with acetyl chloride and benzoyl chloride in pyridine to give 4-(2-acetylaminothiazol-4-yl)-3-methyl-5-oxo-1-phenyl-2-pyrazoline (**2a**) and 4-(2-benzoylaminothiazol-4-yl)-3-methyl-5-oxo-1-phenyl-2-pyrazoline (**2b**). Condensation of **1** with aromatic aldehydes, such as benzaldehyde, 4-methoxybenzaldehyde, and 4-nitrobenzaldehyde in ethanol containing a catalytic amount of piperidine afforded the corresponding aldimines 4-(2-arylideneaminothiazol-4-yl)-3-methyl-5-oxo-1-phenyl-2-pyrazoline **3a**–**3c**.

Treatment of **1** with α-haloketones, such as phenacyl bromide following the method of *Saldbolds et al*. [8] yielded the 3-alkyl derivative 4-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-2-imino-3-phenacylthiazole (**4**). However, refluxing **1** with phenacyl bromide or 4-chlorophenacyl bromide in absolute ethanol for a relatively long time produced 3-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-6-phenylimidazo[2,1-*b*]thiazole (**5a**) and 3-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-6-*p*-chlorophenylimidazo[2,1-*b*]thiazole (**5b**).

The reaction of **1** with ethyl cyanoacetate and ethyl acetoacetate in refluxing ethanol afforded the acyl derivatives 3-cyanoacetyl-4-(3-methyl-5-oxo-



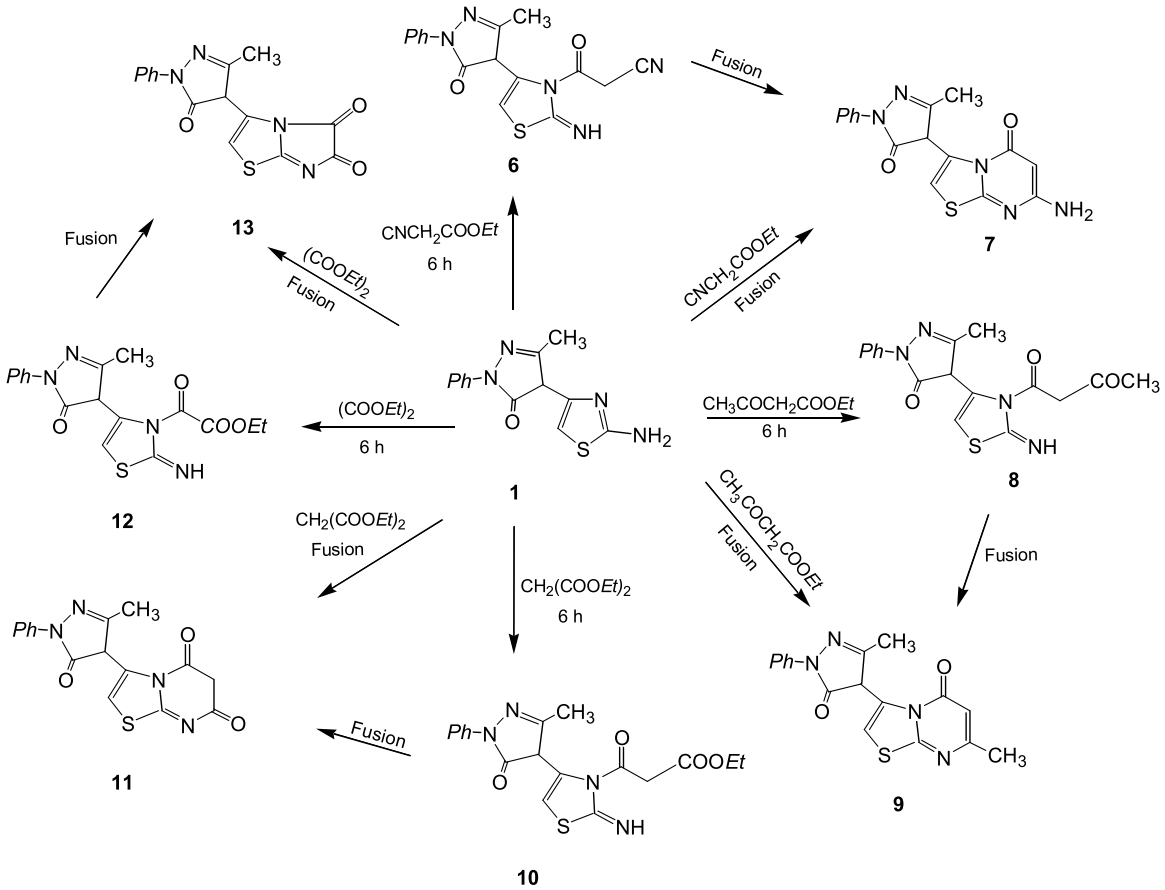
Scheme 1

1-phenyl-2-pyrazolin-4-yl)-2-iminothiazole (**6**) and 3-acetoacetyl-4-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-2-iminothiazole (**8**), which on fusion over its melting point produced 7-amino-3-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)thiazolo[3,2-*a*]-pyrimidin-5-one (**7**) and 7-methyl-3-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)thiazolo[3,2-*a*]pyrimidin-5-one (**9**). Morever, when the reaction was carried out by simple fusion of **1** with ethyl cyanoacetate or ethyl acetoacetate it afforded the cyclized product **7** and **9** directly. Applying this reaction to diethyl malonate gave 5,7-(6*H*)-dioxo-3-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)thiazolo[3,2-*a*]-pyrimidine (**11**) through the intermediate **10**, and when it reacted with diethyl oxalate in an analogous way it gave 5,6-dioxo-3-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)imidazo[2,1-*b*]thiazole (**13**) through the intermediate **12**.

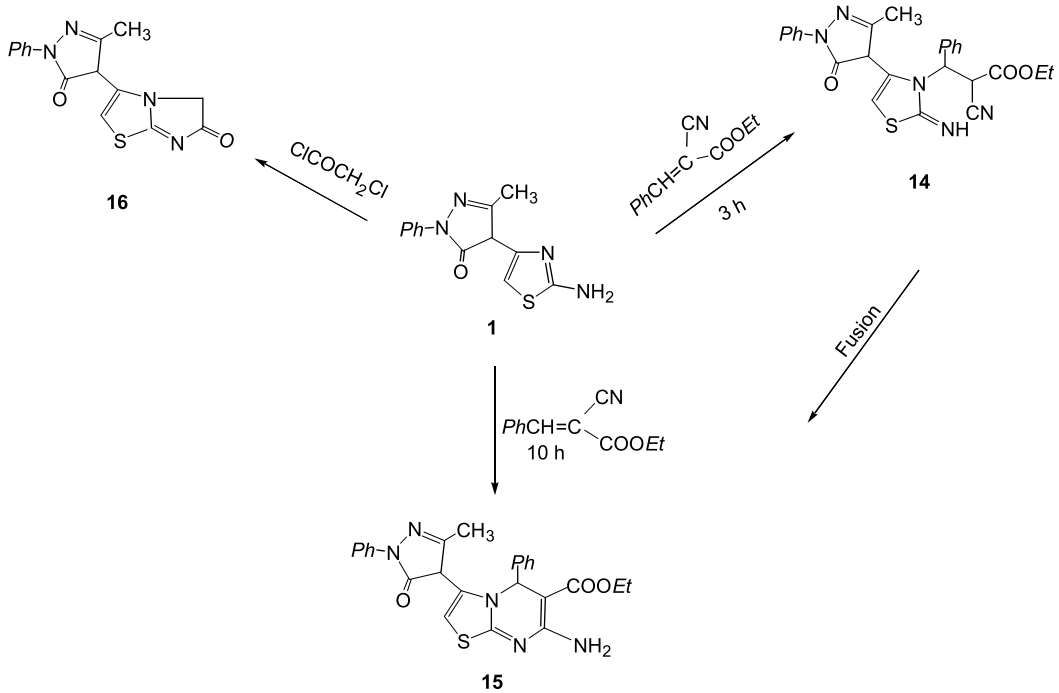
Compound **1** was also subjected to the reaction with arylidene compounds. Thus, it was found that **1** reacts with ethyl benzylidenecyanoacetate to afford 7-amino-6-carboethoxy-3-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-5-phenylthiazolo[3,2-*a*]pyrimidine (**15**) through the formation of the intermediate **14**, which could also be separated. Compound **1** treated with chloroacetyl chloride in absolute ethanol provided 3-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-imidazo[2,1-*b*]thiazol-6-one (**16**). 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). Compound **11** showed a wide spectrum of antifungal action but a narrow spectrum of antibacterial effects with minimum inhibitory concentrations (*MIC*) ranging from 5 to 50 mg/cm^3 (Table 1). Compound **16** exhibited good activity against three pathogenic fungi *Candida albicans*, *Geotrichum candidum*, and *Scopulariopsis brevicaulis* in addition to four pathogenic bacteria



Scheme 2



Scheme 3

Table 1 The Minimum inhibitory concentrations ($MIC/\mathrm{mg\,cm^{-3}}$) of the compounds tested

Organisms	Compounds										
	1	**5b**	**6**	**7**	**11**	**12**	**13**	**14**	**15**	**16**	**Ref.***
Fungi											
Aspergillus flavus	–	–	–	–	50	–	–	–	–	–	10
Aspergillus niger	–	–	–	–	50	–	–	–	–	–	10
Candida albicans	–	–	–	–	50	–	–	–	–	20	10
Geotrichum candidum	–	10	20	–	50	10	10	20	20	10	10
Scopulariopsis brevicaulis	–	–	–	–	50	–	–	–	–	20	10
Trichophyton rubrum	–	–	–	–	50	–	–	–	–	–	10
Bacteria											
Bacillus cereus (*Gram* positive)	10	2	20	10	50	10	50	10	10	2	10
Staphylococcus aureus (*Gram* positive)	10	5	–	50	50	20	–	–	20	5	10
Pseudomonas aeruginosa (*Gram* negative)	–	–	–	–	–	–	–	–	–	20	10
Serratia marcescens (*Gram* negative)	–	–	–	–	–	–	–	–	–	20	10
Escherichia coli (*Gram* negative)	–	–	–	–	–	–	–	–	–	–	10

* **Ref**. Reference drugs = (chloramphenicol as antibacterial and clotrimazole as antifungal)
– No antimicrobial action

Bacillus cereus, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Serratia marcescens* with *MIC*s ranging from 2 to 20 $\mathrm{mg/cm^3}$. 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 $\mathrm{mg/cm^3}$. 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* and *S. marcescens* which were inhibited by **16** (*MIC* 20 $\mathrm{mg/cm^3}$). Among the tested fungi *G. candidum* was the most sensitive organism to the compounds tested. Comparing the *MIC* of the effective compounds with those of the reference drugs (clotrimazole as antifungal and chloramphenicol as antibacterial) revealed that **5b** and **16** were effective against *Gram* positive bacteria at concentrations ranging from 2 to 5 $\mathrm{mg/cm^3}$, which are significantly lower than the *MIC* of chloramphenicol (10 $\mathrm{mg/cm^3}$). Otherwise the *MIC* of the antimicrobial compounds was equal or higher than those of the reference drugs.

Experimental

Melting points were determined on APP. Digital ST 15 melting point apparatus and are corrected. 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. ^{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 a JOEL JMS 600 spectrometer.

4-(2-Acetylaminothiazol-4-yl)-3-methyl-5-oxo-1-phenyl-2-pyrazoline (**2a**, $C_{15}H_{14}N_4O_2S$)

A mixture of 2.72 g **1** [7] (10 mmol) and 1.56 g acetyl chloride (20 mmol) in 20 $\mathrm{cm^3}$ pyridine was refluxed for 3 h. The reaction mixture was added to cold water, the solid so obtained was collected by filtration, dried, and crystallized from ethanol to give 2.19 g (70%) **2a**. Mp 184°C; ^{1}H NMR (90 MHz, *DMSO*-d_6): $\delta = 2.40$ (s, CH_3), 6.70 (s, NH), 7.11 (s, CH-thiazole), 7.41–8.10 (m, *Ar*–H, H-pyrazole) ppm; IR (KBr): $\bar{\nu} = 3400$ (NH), 3100 (CH aliphatic), 1710 (C=O acetyl), 1705 (C=O) $\mathrm{cm^{-1}}$.

4-(2-Benzoylaminothiazol-4-yl)-3-methyl-5-oxo-1-phenyl-2-pyrazoline (**2b**, $C_{20}H_{16}N_4O_2S$)

A mixture of 2.72 g **1** (10 mmol) and 2.52 g benzoyl chloride (20 mmol) in 20 $\mathrm{cm^3}$ pyridine was refluxed for 3 h. The reaction mixture was added to cold water, the solid so obtained was collected by filtration, dried, and crystallized from ethanol to give 2.66 g (71%) **2b**. Mp 220°C; ^{1}H NMR (90 MHz, *DMSO*-d_6): $\delta = 2.35$ (s, CH_3), 6.70 (s, NH), 7.11 (s, CH-thiazole), 7.41–8.10 (m, *Ar*–H, H-pyrazole) ppm; IR (KBr): $\bar{\nu} = 3400$ (NH), 3100 (CH aliphatic), 1710 (C=O benzoyl), 1705 (C=O) $\mathrm{cm^{-1}}$.

*General procedure of the reaction of 4-(2-aminothiazol-4-yl)-3-methyl-5-oxo-1-phenyl-2-pyrazoline with aromatic aldehydes **3a–3c***

To a mixture of 2.72 g **1** (10 mmol) in 25 cm^3 absolute ethanol and 1.06 g benzaldehyde (10 mmol) or 1.36 g 4-methoxybenzaldehyde (10 mmol) or 1.51 g 4-nitrobenzaldehyde (10 mmol), a few drops of piperidine were added. The reaction mixture was heated under reflux for 5 h, added to cold water, the precipitate was collected by filtration, and dried. Compound **3a** was crystallized from toluene to give 2.70 g (75%), **3b** was crystallized from pet ether (60–80°C) to give 2.82 g (72%), and **3c** crystallized from toluene to give 3.15 g (78%).

2-Benzylideneamino-4-(3-methoxy-1-phenyl-5-oxo-2-pyrazolin-4-yl)thiazole (**3a**, $C_{20}H_{16}N_4OS$)

Mp 200°C; ^{1}H NMR (90 MHz, $CDCl_3$): $\delta = 2.40$ (s, CH_3), 3.00 (s, CH), 7.11 (s, CH-thiazole), 7.41–8.10 (m, *Ar*–H, H-pyrazole) ppm; IR (KBr): $\bar{\nu} = 3100$ (CH-aliphatic), 1705 (C=O), 1590 (C=N) cm^{-1}.

2-p-Methoxybenzylideneamino-4-(3-methoxy-1-phenyl-5-oxo-2-pyrazolin-4-yl)thiazole (**3b**, $C_{21}H_{18}N_4O_2S$)

Mp 220°C; ^{1}H NMR (90 MHz, $CDCl_3$): $\delta = 2.90$ (s, CH_3), 3.00 (s, CH), 3.20 (s, CH_3), 7.11 (s, CH-thiazole), 7.41–8.10 (m, *Ar*–H, H-pyrazole) ppm; IR (KBr): $\bar{\nu} = 3100$ (CH-aliphatic), 1705 (C=O), 1590 (C=N) cm^{-1}.

2-p-Nitrobenzylideneamino-4-(3-methoxy-1-phenyl-5-oxo-2-pyrazolin-4-yl)thiazole (**3c**, $C_{20}H_{15}N_5O_3S$)

Mp 210°C; ^{1}H NMR (90 MHz, $CDCl_3$): $\delta = 2.40$ (s, CH_3), 3.00 (s, CH), 7.11 (s, CH-thiazole), 7.41–8.10 (m, *Ar*–H, H-pyrazole) ppm; IR (KBr): $\bar{\nu} = 3100$ (CH-aliphatic), 1705 (C=O), 1590 (C=N) cm^{-1}.

4-(3-Methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-2-imino-3-phenacylthiazole (**4**, $C_{21}H_{18}N_4O_2S$)

A mixture of 2.72 g **1** (10 mmol) and 1.99 g 2-bromoacetophenone (10 mmol) in 30 cm^3 absolute ethanol was refluxed for 3 h. The reaction mixture was cooled, poured into cold water, and neutralized with potassium carbonate; the solid thus obtained was crystallized from ethanol to give 2.92 g (75%) **4**. Mp 158°C; ^{1}H NMR (90 MHz, *DMSO*-d_6): $\delta = 2.45$ (s, CH_3), 3.20 (s, CH_2), 6.70 (s, NH), 7.11 (s, CH-thiazole), 7.41–8.10 (m, *Ar*–H, H-pyrazole) ppm; IR (KBr): $\bar{\nu} = 3400$ (NH), 3100 (CH-aliphatic), 1710 (C=O ketone), 1705 (C=O), 1590 (C=N) cm^{-1}.

*3-(3-Methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-6-arylimidazo-[2,1-b]thiazole (**5a**, **5b**)*

A mixture of 2.72 g **1** (10 mmol) and 1.99 g 2-bromoacetophenone (10 mmol) or 2.33 g 4-chloro-2-bromoacetophenone (10 mmol) in 30 cm^3 absolute ethanol was refluxed for 6 h. The reaction mixture was concentrated, cooled, poured into cold water, and neutralized with potassium carbonate. Compound **5a** was crystallized from ethanol to give 2.67 g (72%) and **5b** was crystallized from ethanol to give 3.16 g (72%).

3-(3-Methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-6-phenyl-imidazo[2,1-b]thiazole (**5a**, $C_{21}H_{16}N_4OS$)

Mp 291°C; ^{1}H NMR (90 MHz, *DMSO*-d_6): $\delta = 2.40$ (s, 3H, CH_3), 3.20 (s, 3H, CH_3), 6.81 (s, 1H, CH-imidazole), 7.11 (s, 1H, CH-thiazole), 7.41–8.10 (m, 11H, *Ar*–H and H-pyrazole) ppm; IR (KBr): $\bar{\nu} = 3100$ (CH-aliphatic), 1705 (C=O) cm^{-1}.

3-(3-Methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-6-p-chlorophenylimidazo[2,1-b]thiazole (**5b**, $C_{21}H_{15}N_4OSCl$)

Mp 285°C; ^{1}H NMR (90 MHz, *DMSO*-d_6): $\delta = 2.40$ (s, CH_3), 3.20 (s, CH_3), 6.81 (s, CH-imidazole), 7.11 (s, CH-thiazole), 7.41–8.10 (m, *Ar*–H and H-pyrazole) ppm; IR (KBr): $\bar{\nu} = 3100$ (CH-aliphatic), 1705 (C=O) cm^{-1}.

3-Cyanoacetyl-4-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-2-iminothiazole (**6**, $C_{16}H_{13}N_5O_2S$)

A mixture of 2.72 g **1** (10 mmol) and 1.13 g ethyl cyanoacetate (10 mmol) in 30 cm^3 absolute ethanol was refluxed for 6 h. The reaction mixture was then cooled, the solid precipitate was filtered off, dried, and crystallized from toluene to give 2.64 g (78%) **6**. Mp 256°C; ^{1}H NMR (90 MHz, $CDCl_3$): $\delta = 2.40$ (s, CH_3), 3.20 (s, CH_2), 6.70 (s, NH), 7.11 (s, CH-thiazole), 7.41–8.10 (m, *Ar*–H and H-pyrazole) ppm; IR (KBr): $\bar{\nu} = 3400$ (NH), 3100 (CH-aliphatic), 2200 (CN), 1710 (C=O ketone), 1705 (C=O), 1590 (C=N) cm^{-1}.

7-Amino-4-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-thiazolo[3,2-a]pyrimidin-5-one (**7**, $C_{16}H_{13}N_5O_2S$)

A mixture of 2.72 g **1** (10 mmol) and 1.13 g ethyl cyanoacetate (10 mmol) was heated at 240°C in an oil bath for 3 h. The reaction mixture was allowed to cool to afford a solid residue. Washing several times with pet ether (60–80°C) and crystallization from ethanol gave 2.54 g (75%) **7**. Mp 286°C; ^{1}H NMR (90 MHz, $CDCl_3$): $\delta = 2.40$ (s, CH_3), 6.11 (s, CH-pyrimidine), 6.70 (s, NH_2), 7.11 (s, CH-thiazole), 7.41–8.10 (m, *Ar*–H and H-pyrazole) ppm; IR (KBr): $\bar{\nu} = 3250$–3400 (NH_2), 3100 (CH-aliphatic), 1720 (C=O ketone), 1705 (C=O) cm^{-1}.

*Another route for the preparation of **7***

Compound **6**, 1.61 g (5 mmol), was heated at 255°C in an oil bath for 1 h and was allowed to cool, washed with with pet ether (60–80°C), and crystallized from ethanol. It was found that the product was identical in all aspects (mp, mixed mp, IR, and ^{1}H NMR) with **7**.

3-Acetoacetyl-3-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-2-iminothiazole (**8**, $C_{17}H_{16}N_4O_3S$)

A mixture of 2.72 g **1** (10 mmol) and 1.30 g ethyl acetoacetate (10 mmol) in 30 cm^3 absolute ethanol was refluxed for 6 h. The reaction mixture was allowed to cool and poured into cold water, the solid was obtained, filtered off, dried, and crystallized from toluene to give 2.52 g (71%) **8**. Mp 285°C; ^{1}H NMR (90 MHz, *DMSO*-d_6): $\delta = 2.45$ (s, CH_3), 3.00 (s, CH_3), 3.30 (s, CH_2), 6.70 (s, NH), 7.11 (s, CH-thiazole), 7.41–8.10 (m, *Ar*–H and H-pyrazole) ppm; IR (KBr): $\bar{\nu} =$ 3400 (NH), 3100 (CH aliphatic), 1720 (C=O ketone), 1710 (C=O ketone), 1705 (C=O) cm^{-1}.

7-Methyl-3-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)thiazolo[3,2-a]pyrimidin-5-one (**9**, $C_{17}H_{14}N_4O_2S$)
A mixture of 2.72 g **1** (10 mmol) and 1.30 g ethyl acetoacetate (10 mmol) was heated at 240°C in an oil bath for 3 h. The reaction mixture was allowed to cool to afford a solid residue, washed several times with pet ether (60–80°C), and crystallized from ethanol to give 2.43 g (72%) **9**. Mp 296°C; ^{1}H NMR (90 MHz, $CDCl_3$): $\delta = 1.80$ (s, CH_3-pyrimidine), 2.40 (s, CH_3), 6.11 (s, CH-pyrimidine), 7.11 (s, CH-thiazole), 7.41–8.10 (m, *Ar*–H, H-pyrazole) ppm; IR (KBr): $\bar{\nu} = 3100$ (CH-aliphatic), 1720 (C=O ketone), 1705 (C=O) cm^{-1}.

*Another route for the preparation of **9***
Compound **8**, 1.78 g (5 mmol), was heated at 265°C in an oil bath for 1 h and was allowed to cool, washed with pet ether (60–80°C), and crystallized from ethanol, It was found that the product was identical in all aspects (mp, mixed mp, IR, ^{1}H NMR) with **9**.

3-Carboethoxyacetyl-3-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-2-iminothiazole (**10**, $C_{18}H_{18}N_4O_4S$)
A mixture of 2.72 g **1** (10 mmol) and 1.61 g diethyl malonate (10 mmol) in 30 cm^3 absolute ethanol was refluxed for 6 h. The reaction mixture was allowed to cool and poured into cold water, the solid was obtained, filtered off, dried, and crystallized from ethanol to give 2.77 g (72%) **10**. Mp 262°C; ^{1}H NMR (90 MHz, *DMSO*-d_6): $\delta = 1.20$ (t, CH_3), 2.45 (s, CH_3), 3.00 (q, CH_2), 3.60 (s, CH_2), 6.70 (s, NH), 7.11 (s, CH-thiazole), 7.41–8.10 (m, *Ar*–H, H-pyrazole) ppm; IR (KBr): $\bar{\nu} = 3400$ (NH), 3100 (CH-aliphatic), 1730 (C=O ester), 1710 (C=O ketone), 1705 (C=O) cm^{-1}.

5,7-(6H)-Dioxo-3-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)thiazolo[3,2-a]pyrimidine (**11**, $C_{16}H_{11}N_4O_3S$)
A mixture of 2.72 g **1** (10 mmol) and 1.61 g diethyl malonate (10 mmol) was heated at 240°C in an oil bath for 3 h. The reaction mixture was allowed to cool to afford a solid residue, washed several times with pet ether (60–80°C) and crystallized from ethanol to give 2.50 g (73%) **11**. Mp 290°C; ^{1}H NMR (90 MHz, $CDCl_3$): $\delta = 2.40$ (s, CH_3), 6.31 (s, CH_2-pyrimidine), 7.11 (s, CH-thiazole), 7.41–8.10 (m, *Ar*–H, H-pyrazole) ppm; IR (KBr): $\bar{\nu} = 3100$ (CH-aliphatic), 1725 (C=O ketone), 1720 (C=O ketone), 1705 (C=O) cm^{-1}.

*Another route for the preparation of **11***
Compound **10**, 1.93 g (5 mmol), was heated at 275°C in an oil bath for 1 h and was allowed to cool, washed with pet ether (60–80°C), and crystallized from ethanol. It was found that the product was identical in all aspects (mp, mixed mp, IR, ^{1}H NMR) with **11**.

3-Carboethoxycarbonyl-3-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-2-iminothiazole (**12**, $C_{17}H_{16}N_4O_4S$)
A mixture of 2.72 g **1** (10 mmol) and 1.23 g diethyl oxalate (10 mmol) in 30 cm^3 absolute ethanol was refluxed for 6 h. The reaction mixture was allowed to cool and poured into cold water, the solid was obtained, filtered off, dried, and crystallized from toluene to give 2.75 g (74%) **12**. Mp 272°C; ^{1}H NMR (90 MHz, *DMSO*-d_6): $\delta = 1.35$ (t, CH_3), 2.45 (s, CH_3), 3.10 (q, CH_2), 6.70 (s, NH), 7.11 (s, CH-thiazole), 7.41–8.10 (m, *Ar*–H, H-pyrazole) ppm; IR (KBr): $\bar{\nu} = 3400$ (NH), 3100 (CH-aliphatic), 1730 (C=O ester), 1710 (C=O ketone), 1705 (C=O) cm^{-1}.

5,6-Dioxo-3-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-imidazo[2,1-b]thiazole (**13**, $C_{15}H_{10}N_4O_3S$)
A mixture of 2.72 g **1** (10 mmol) and 1.23 g diethyl oxalate (10 mmol) was heated at 240°C in an oil bath for 3 h. The reaction mixture was allowed to cool to afford a solid residue, washed several times with pet ether (60–80°C) and crystallized from ethanol to give 2.54 g (78%) **13**. Mp 300°C; ^{1}H NMR (90 MHz, $CDCl_3$): $\delta = 2.40$ (s, CH_3), 7.11 (s, CH-thiazole), 7.41–8.10 (m, *Ar*–H and H-pyrazole) ppm; IR (KBr): $\bar{\nu} = 3100$ (CH aliphatic), 1720 (C=O ketone), 1715 (C=O ketone), 1705 (C=O) cm^{-1}.

*Another route for the preparation of **13***
Compound **12**, 1.86 g (5 mmol), was heated at 280°C in an oil bath for 1 h and was allowed to cool, washed with pet ether (60–80°C), and crystallized from ethanol. It was found that the product was identical in all aspects (mp, mixed mp, IR, ^{1}H NMR) with **13**.

Ethyl 7-amino-3-[2-imino-4-(3-methyl-1-phenyl-5-oxo-2-pyrazolin-4-yl)-3H-thiazol-3-yl]-3-phenyl-2-cyanopropanate (**14**, $C_{25}H_{23}N_5O_3S$)
A mixture of 2.72 g **1** (10 mmol) and 2.01 g ethyl benzylidenecyanoacetate (10 mmol) in 30 cm^3 absolute ethanol containing 5 drops of piperidine as catalyst was refluxed for 3 h. The reaction mixture was poured into cold water and the solid precipitate was collected by filteration, dried, and crystallized from ethanol to give 3.59 g (76%) **14**. Mp 267°C; ^{1}H NMR (90 MHz, $CDCl_3$): $\delta = 1.20$ (t, CH_3 ester), 2.45 (s, CH_3), 2.70 (d, CH), 2.75 (d, CH), 3.00 (q, CH_2 ester), 6.70 (s, NH), 7.11 (s, CH-thiazole), 7.41–8.10 (m, *Ar*–H, H-pyrazole) ppm; IR (KBr): $\bar{\nu} = 3400$ (NH), 3100 (CH-aliphatic), 2200 (CN), 1730 (C=O ester), 1705 (C=O) cm^{-1}.

7-Amino-6-carboethoxy-3-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-5-phenylthiazolo[3, 2-a] pyrimidine (**15**, $C_{25}H_{23}N_5O_3S$)
A mixture of 2.72 g **1** (10 mmol) and 2.01 g ethyl benzylidenecyanoacetate (10 mmol) in 30 cm^3 absolute ethanol with 5 drops of piperidine as catalyst was refluxed for 10 h. The reaction mixture was poured into cold water and the solid precipitate was collected by filtration, dried, and crystallized from toluene to give 3.35 g (71%) **15**. Mp 297°C; ^{1}H NMR (90 MHz, *DMSO*-d_6): $\delta = 1.20$ (t, CH_3 ester), 2.45 (s, CH_3), 3.00 (q, CH_2 ester), 6.11 (s, CH-pyrimidine), 6.70 (s, NH_2), 7.11 (s, CH-thiazole), 7.41–8.10 (m, *Ar*–H, H-pyrazole) ppm; IR (KBr): $\bar{\nu} = 3300$–3400 (NH_2), 3100 (CH aliphatic), 1730 (C=O ester), 1705 (C=O) cm^{-1}.

*Another route for the preparation of **15***
Compound **14**, 2.36 g (5 mmol), was heated at 290°C in an oil bath for 1 h and was allowed to cool, washed with petroleum

ether (60–80°C), and crystallized from toluene. It was found that the product was identical in all aspects (mp, mixed mp, IR, and ^{1}H NMR) with **15**.

3-(3-Methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)imidazo[2,1-b]-thiazol-6-one (**16**, $C_{15}H_{11}N_4O_2S$)
A mixture of 2.72 g **1** (10 mmol) and 0.79 cm^3 chloroacetyl chloride (10 mmol) in 30 cm^3 absolute ethanol was refluxed for 6 h and then cooled. The solid precipitate was collected, dried, and crystallized from ethanol to give 2.33 g (73%) **16**. Mp 265°C; ^{1}H NMR (90 MHz, $CDCl_3$): $\delta = 2.21$ (s, CH_3), 6.31 (s, CH_2-imidazole), 7.11 (s, CH-thiazole), 7.41–8.10 (m, *Ar*–H and H-pyrazole) ppm; IR (KBr): $\bar{\nu} = 1715$ (C=O), 1705 (C=O) cm^{-1}.

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