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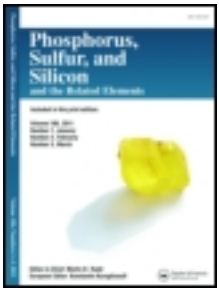

Phosphorus, Sulfur, and Silicon and the Related Elements

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Synthesis and Antimicrobial Activity of Some New 1,3-Diphenylpyrazoles Bearing Pyrimidine, Pyrimidinethione, Thiazolopyrimidine, Triazolopyrimidine, Thio-and Alkylthiotriazolop-Yrimidinone Moieties at the 4-Position

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Synthesis and Antimicrobial Activity of Some New 1,3-Diphenylpyrazoles Bearing Pyrimidine, Pyrimidinethione, Thiazolopyrimidine, Triazolopyrimidine, Thio- and Alkylthiotriazolop-Yrimidinone Moieties at the 4-Position

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*1,3-diphenyl-1H-pyrazole-4-carboxaldehyde (**1**) reacted with ethyl cyanoacetate and thiourea to give the pyrimidinethione derivative **2**. The reaction of **2** with some alkylating agents gave the corresponding thioethers **3a–e** and **7**. Thione **2** was cyclized to **5** and **6** upon a reaction with chloroacetic acid and with benzaldehyde, respectively. Thioether **3c** was cyclized to **4** upon boiling with sodium acetate in ethanol, and **7** was cyclized to **8** upon boiling in an acetic anhydride-pyridine mixture. The hydrazino derivative **9** was prepared either by boiling **2** and/or **3a** with hydrazine. The reaction of **9** with nitrous acid, acetylacetone, triethyl orthoformate, acetic anhydride, and carbon disulfide gave **10–14**. The alkylation of **14** with ethyl iodide, phenacyl bromide, and ethyl chloroacetate afforded the alkythiotriazolo pyrimidinone derivatives **15a–c**. The dialkyl derivative **16** was produced upon the treatment of **2** with two equivalents of ethyl iodide. Boiling **16** with hydrazine afforded the hydrazino **17**. The reaction of **17** with nitrous acid, carbon disulfide, ethyl cyanoacetate, ethyl acetoacetae, and phenacyl bromide gave **18–22**, respectively. Some of the newly obtained compounds were tested for their antibacterial and antifungal activities.*

Keywords 1,3-diphenylpyrazole; pyrimidine; pyrimidinethione; thiazolopyrimidine; thio- and alkylthiotriazolpyrimidinone; triazolopyrimidine

INTRODUCTION

The chemistry of the pyrazole nucleus has received much more attention during the last few decades,[1–9] because of outstanding biological activities. It acts as antipyretic, analgesic, antiinflammatory,[10–13] antianxiety,[14] kinase inhibitors,[15–18] and as insecticides.[19] It has good properties as antibacterial, antifungal, and an antiparasitic, as well.[20–30] Considering all of these benefits and in continuation of our

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work to synthesize new heterocycles starting from 1,3-diphenyl-1*H*-pyrazole-4-carboxaldehyde,[27,28] we introduce herein several new pharmacophores, such as pyrimidine, pyrimidinethione, thiazolopyrimidine, triazolopyrimidine, and tetrazolopyrimidine moieties onto the pyrazole nucleus in an effort to obtain compounds with enhanced potency. Some of the synthesized compounds were screened in vitro for their antibacterial and antifungal activities.

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RESULTS AND DISCUSSION

A one-pot reaction of 1,3-diphenyl-1*H*-pyrazole-4-carboxaldehyde (**1**), ethyl cyanoacetate, and thiourea in absolute ethanol in the presence of potassium carbonate gave 6-(1,3-diphenyl-1*H*-pyrazolo-4-yl)-5-cyano-4-oxo-1,2,3,4-tetrahydropyrimidine-2-thione (**2**). The alkylaion of **2** with some alkylating agents, namely ethyl iodide, benzyl chloride, phenacyl bromide, ethyl chloroacetate, and chloroacetonitrile, gave the alkylated products **3a–e**. Allowing **3c** to be heated under reflux in ethanol in the presence of anhydrous sodium acetate for 10 h led to a ring closure and the formation of the thiazolopyrimidinone derivative **4** (Scheme 1).

The ternary condensation of **2**, chloroacetic acid, and benzaldehyde, in presence of fused sodium acetate and acetic anhydride, resulted in the formation of 2-benzylidene-7-(1,3-diphenyl-1-*H*-pyrazol-4-yl)-2,3-dihydro-6-cyanothiazolo[3,2-a]pyrimidin-3,5-dione **6**. When the reaction was performed without benzaldehyde, the product was identified as thiazolopyrimidine derivative **5**. Compound **6** had been independently synthesized through the interaction of **5** with benzaldehyde in the presence of a catalytic amount of piperidine (Scheme 1).

The intermediate 6-(1,3-diphenyl-1*H*-pyrazol-4-yl)-2(3-pentan-2,4-dione)thio-5-cyano pyrimidin-4(3*H*)-one (**7**) was obtained when 2 was alkylated with 3-chloroacetylacetone at r.t. in ethanol in the presence of potassium hydroxide. Boiling **7** in a mixture of acetic anhydride and pyridine (1:1) gave rise to the thiazolopyrimidine derivative **8** (Scheme 1).

The formation of the hydrazinopyrimidineone **9** was achieved either by heating **2** with hydrazine hydrate in pyridine under reflux for 6 h or by heating **3**a with hydrazine hydrate in absolute ethanol for 10 h[29] (Scheme 2).

The synthetic potency of the hydrazino group of **9** was examined with some reagents in mind to synthesize new 1,3-diphenylpyrazole members bearing substituted pyrimidinonone, triazolopyrmidinone, and triazolopyrmidinonethione groups at position 4. Thus, the treatment of **9** with nitrous acid[30] afforded the azidopyrimidinone derivative **10** in a

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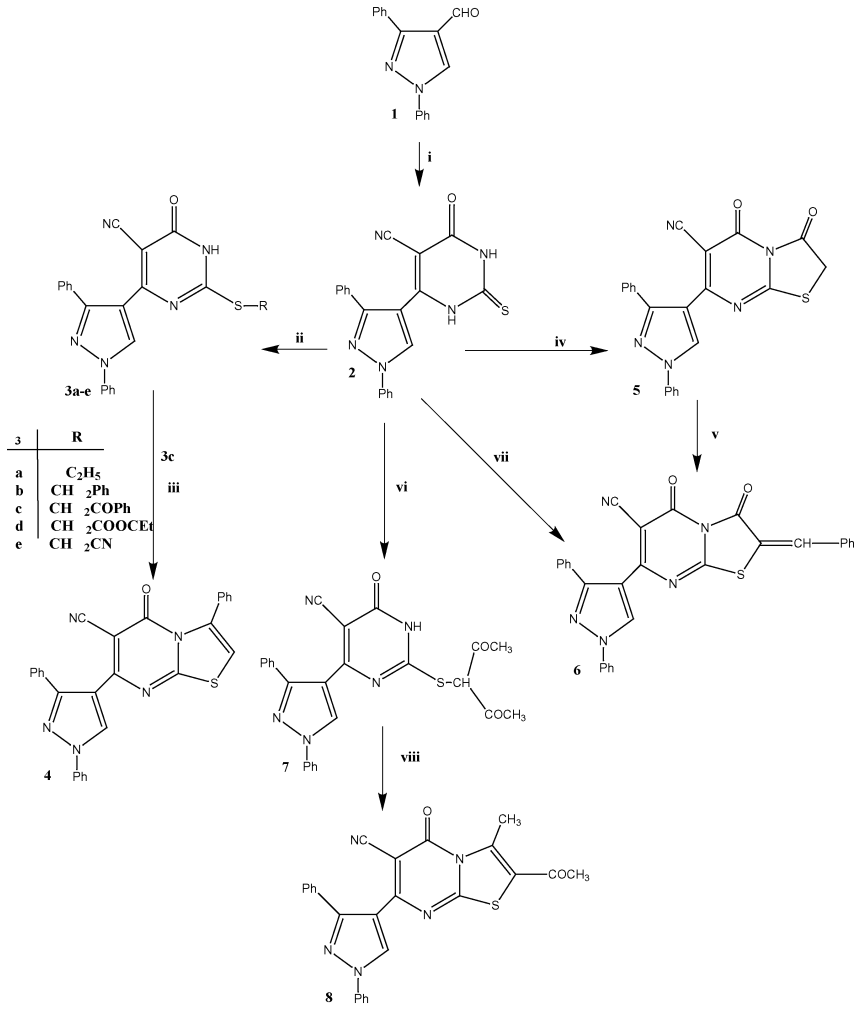
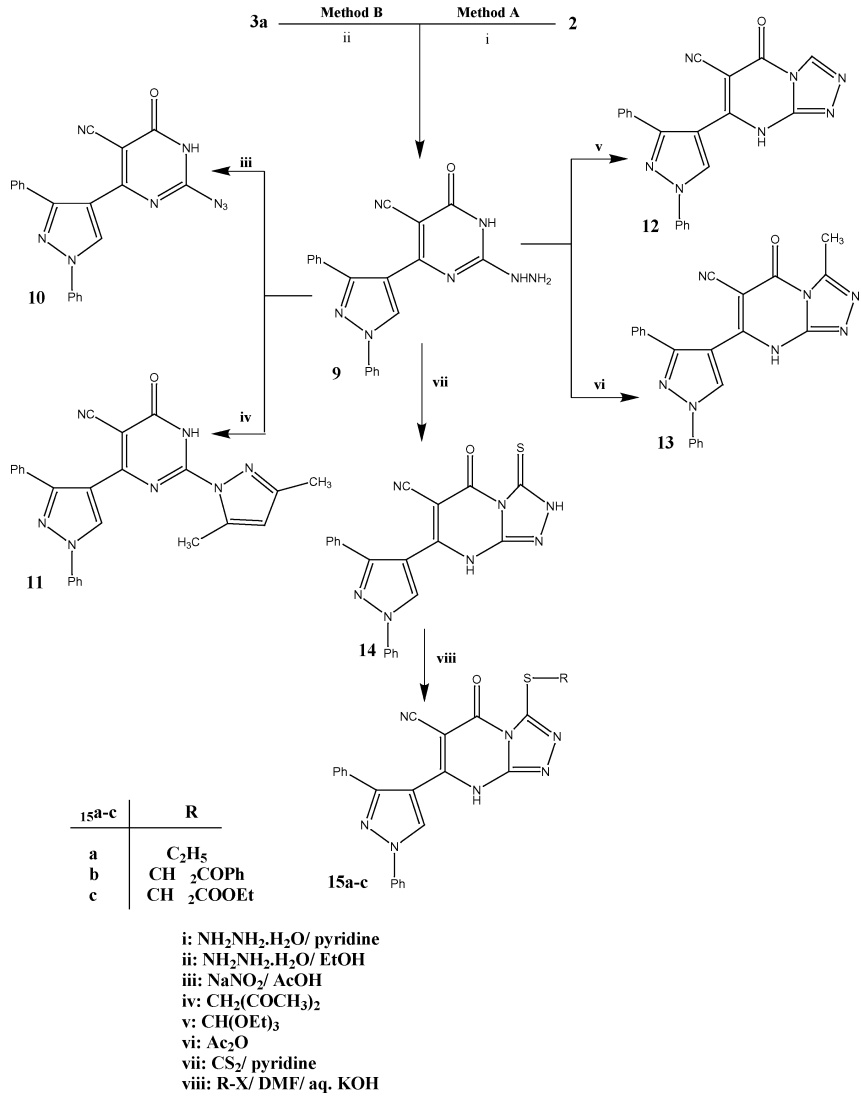


SCHEME 1

moderate yield. The IR spectrum of **10** showed an absorption band at 2180 cm^{-1}, which is characteristic for the azido group. The condensation of **9** with acetylacetone[29] gave the dimethylpyrazolyl derivative **11**. Boiling **9** in triethyl orthoformate and in acetic anhydride gave the triazolopyrimidinone derivatives **12** and **13**, respectively (Scheme 2). The



SCHEME 2

thione derivative **14** was obtained when **9** was interacted with carbon disulfide in pyridine. The alkylation of **14** using ethyl iodide, phenacyl bromide, and ethyl chloroacetate gave the alkylthiotriazolpyrimidinone derivatives **15a–c** (Scheme 2).

The dialkylation of **2** using two equivalents of ethyl iodide gave 6-(1,3-diphenyl-1H-pyrazol-4-yl)-5-cyano-3-ethyl-4-oxo-1,2,3,4-tetrahydropyrimidine-2-ethylthio **(16)** (Scheme 2).

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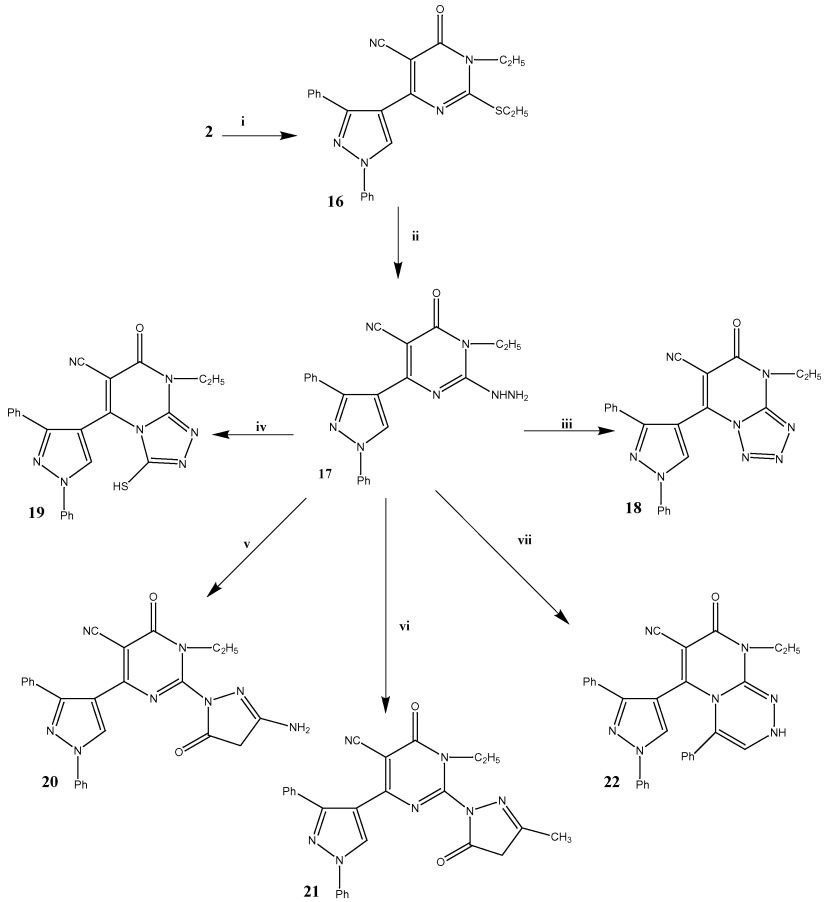
The replacement of the ethylthio group of **16** by the hydrazine group[30] had been achieved when the later was heated under reflux with hydrazine hydrate in ethanol for 10 h to give the hydrazino derivative **17**. Compound **17** is a key intermediate for producing new fused and unfused heterocycles. Thus, upon the reaction of **17** with nitrous acid, carbon disulfide, ethyl cyanoacetate, ethyl acetoacetate, and phenacyl bromide, the tetrazolopyrimidine **18**, the mercaptptriazolopyrimidine **19**, the dipyrazolyl derivatives **20–21**, and the triazinopyrimidine **22** were produced, respectively (Scheme 3).



SCHEME 3

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EXPERIMENTAL

M.p.s were uncorrected and determined using a Kofler m.p. apparatus. IR spectra were recorded on a Pye Unicam SP 3-100 spectrophotometer using the KBr wafer technique. ^{1}H NMR spectra were recorded on a Varian EM-390 90 MHz spectrometer using TMS as an internal standard. MS spectra were measured on SSQ-7000 apparatus at 70 eV. Elemental analyses were carried out at the Microanalytical Center of Cairo University (Cairo, Egypt) and at the Microanalytical unit at Assuit University (Assuit, Egypt). The characterization data of all newly synthesized compounds are given in Table I.

1,3-Diphenyl-1H-pyrazole-4-carboxaldehyde (1)

This compound was prepared according to a reported method.[32]

6-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-5-cyano-4-oxo-1,2,3,4-tetrahydropyrimidine-2-thione (2)

A mixture of 1 (0.01 mol), ethyl cyanoacetate (0.01 mol), thiourea (0.01 mol), and potassium carbonate (0.03 mol) in absolute ethanol (60 mL) was heated under reflux for 12 h, cooled, and neutralized with glacial acetic acid. The product that isolated was crystallized from the proper solvent to give a yellowish-orange **2**. IR (cm^{-1}): 3180 (NH), 2230 (CN), 1670 (CO), 1160 (C=S).^{1}H NMR (DMSO-d_6) δ: 7.3–7.9 (m, 10H, Ar-H), 8.2 (s, 1H, CH-pyrazole), 9.2 (s, 1H, NH), 9.8 (s, 1H, NH).

The Alkylation of 2: The Formation of Thioethers (3a–e)

A mixture of **2** (0.371 g, 0.001 mol) and alkyl (alkaryl) halides, namely ethyl iodide, benzyl chloride, phenacyl bromide, ethyl chloroacetate, and/or chloroacetonitrile (0.001 mol) in ethanol (30 mL) containing anhydrous sodium acetate (2 g) was refluxed for 2 h and then allowed to cool. The precipitated product was filtered off and recrystallized from the proper solvent.

6-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-5-cyano-4-oxo-1,2,3,4-tetrahydropyrimidine-2-ethylthio (3a)

Pale yellow crystals. IR (cm^{-1}): 3360 (NH), 2200 (CN), 1650 (CO). ^{1}H NMR (DMSO-d_6)δ: 1.2–1.4 (t, 3H, CH_3), 3.5–3.8 (q, 2H, CH_2), 7.2–7.8 (m, 10H, Ar-H), 8.3 (s, 1H, CH-pyrazole), 9.10 (s, 1H, NH).

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TABLE I Analytical Data of the Newly Synthesized Compounds

Compound No.	Yield	Solvent Cryst.	M.P. [°C]	Mol. Formula (Mol. Wt.)	Elemental analyses Calcd./Found (%) C	H	N	S
2	79	methanol	195–196	$C_{20}H_{13}N_5OS$	64.68	3.53	18.86	8.63
				(371.4)	64.37	3.51	19.02	8.88
3a	69	ethanol	.212–13	$C_{22}H_{17}N_5OS$	66.15	4.29	17.53	8.03
				(399.5)	66.50	4.11	17.81	8.34
3b	62	dioxane	187	$C_{27}H_{19}N_5OS$	70.26	4.15	15.18	6.95
				(461.5)	70.40	4.30	15.36	7.07
3c	74	ethanol	262	$C_{28}H_{19}N_5O_2S$	68.70	3.91	14.31	6.55
				(489.6)	69.12	4.12	13.95	6.81
3d	72	ethanol	125–126	$C_{24}H_{19}N_5O_3S$	63.01	4.19	15.31	7.01
				(457.5)	63.41	3.80	15.60	7.35
3e	70	ethanol	149	$C_{22}H_{14}N_6OS$	64.38	3.44	20.48	7.81
				(410.5)	64.77	3.12	20.69	8.20
4	61	ethanol	275–277	$C_{28}H_{17}N_5OS$	71.32	3.63	14.85	6.80
				(471.5)	71.65	3.41	14.70	7.15
5	63	ethanol	> 360	$C_{22}H_{13}N_5O_2S$	64.22	3.18	17.02	7.79
				(411.4)	64.50	3.25	17.38	8.06
6	65	acetic acid	278–280	$C_{29}H_{17}N_5O_2S$	69.73	3.43	14.02	6.42
				(499.5)	70.06	3.12	14.06	6.50
7	69	acetic acid	246–247	$C_{25}H_{19}N_5O_3S$	63.95	4.08	14.92	6.83
				(469.5)	64.37	4.28	15.06	6.61
8	59	dioxane	316–318	$C_{25}H_{17}N_5O_2S$	66.50	3.80	15.51	7.10
				(451.5)	66.10	3.92	15.87	7.50
9	66	dioxane	342–344	$C_{20}H_{15}N_7O$	65.03	4.09	26.54	—
				(369.4)	65.48	4.19	26.10	
10	53	ethanol	311–312	$C_{20}H_{12}N_8O$	63.15	3.18	29.46	—
				(380.4)	62.87	3.44	29.87	
11	93	acetic acid	291–292	$C_{25}H_{19}N_7O$	69.27	4.42	22.62	—
				(433.5)	68.88	4.19	22.61	
12	82	dioxane	> 340	$C_{21}H_{13}N_7O$	66.48	3.45	25.84	—
				(379.4)	66.12	3,41	25.40	
13	63	ethanol	320–322	$C_{22}H_{15}N_7O$	67.17	3.84	24.92	—
				(393.4)	67.42	3.81	25.00	
14	71	dioxane	319–320	$C_{21}H_{13}N_7OS$	61.30	3.18	23.83	7.79
				(411.4)	61.69	3.25	24.10	8.05
15a	62	ethanol	177–179	$C_{23}H_{17}N_7OS$	62.85	3.90	22.31	7.28
				(439.5)	63.12	4.10	22.05	7.66
15b	71	ethanol	197–98	$C_{29}H_{19}N_7O_2S$	65.74	3.63	18.51	6.05
				(529.8)	66.12	3.64	18.60	5.85
15c	72	ethanol	143–145	$C_{25}H_{19}N_7O_3S$	60.35	3.85	19.71	6.44
				(497.5)	60.59	3.81	20.20	6.41
16	64	ethanol	208–210	$C_{24}H_{21}N_5OS$	67.43	4.95	16.38	7.50
				(427.5)	67.12	5.21	16.69	7.88
17	70	acetic acid	301–303	$C_{22}H_{19}N_7O$	66.49	4.82	24.67	—
				(397.4)	66.13	5.01	25.05	—
18	50	benzene	185–187	$C_{22}H_{16}N_8O$	64.70	3.95	27.44	—
				(408.4)	65.05	4.12	27.80	—
19	69	dioxane	266–268	$C_{23}H_{17}N_7OS$	62.86	3.90	22.31	7.30
				(439.5)	63.18	3.91	22.18	7.50
20	52	dioxane	> 300	$C_{25}H_{20}N_8O_2$	64.65	4.34	24.12	—
				(464.5)	64.28	4.12	24.36	—
21	49	dioxane	230–232	$C_{26}H_{21}N_7O_2$	67.38	4.57	21.15	—
				(463.5)	67.70	4.88	21.50	—
22	53	ethanol	> 300	$C_{30}H_{23}N_7O$	72.42	4.66	19.71	—
				(497.6)	72.12	4.80	20.05	—

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6-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-5-cyano-4-oxo-1,2,3,4-tetrahydropyrimidine-2-benzylthio (3b)

Pale yellow crystals. IR (cm^{-1}): 3350 (NH), 2220 (CN), 1660 (CO). ^1H NMR (DMSO-d_6)δ: 3.5 (s, 2H, CH_2), 6.9–7.3 (m, 15H, Ar-H), 8.2 (s, 1H, CH-pyrazole), 9.2 (s, 1H, NH).

6-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-5-cyano-4-oxo-1,2,3,4-tetrahydropyrimidine-2-methylbenzoylthio (3c)

Yellow crystals. IR (cm^{-1}): 3460 (NH),2210 (CN), 1650 (CO). ^1H NMR (DMSO$-d_6$)δ: 4.5 (s, 2H, CH_2), 6.9–7.8 (m, 15H, Ar-H), 8.3 (s, 1H, CH-pyrazole), 9.0 (s, 1H, NH).

Ethyl [6-(1,3-diphenyl-1*H*-pyrazol-4-yl)-5-cyano-4-oxo-1,2,3,4-tetrahydropyrimidine-2-thio]acetate (3d)

Yellow crystals. IR (cm^{-1}): 3290 (NH), 2215 (CN), 1730 (CO), 1650 (CO).^1H NMR (DMSO-d_6)δ: 1.3–1.5 (t, 3H, $CO_2CH_2CH_3$), 3.9–4.2 (q, 2H, $CO_2CH_2CH_3$), 4.6 (s, 2H, CH_2), 7.2–7.8 (m, 10H, Ar-H), 8.3 (s, 1H, CH-pyrazole), 9.1 (s, 1H, NH). MS: m/z 457.12 (M^+, 9.50%).

6-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-5-cyano-4-oxo-1,2,3,4-tetrahydro pyrimidine-2-cyanomethylthio (3e)

Yellow crystals. IR (cm^{-1}): 3220 (NH), 2220 (CN),1680 (CO). ^1H NMR (DMSO$-d_6$)δ: 3.3 (s, 2H, CH_2), 7.2–7.8 (m, 10H, Ar-H), 8.3 (s, 1H, CH-pyrazole), 8.9 (s, 1H, NH).

7-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-3-phenyl-6-cyanothiazolo[3,2-a]pyrimidin-5-one (4)

A mixture of **3c** (0.001 mol) and anhydrous sodium acetate (2 g) in ethanol (30 mL) was heated under reflux for 10 h and then left to cool. The precipitated solid was collected and recrystallized from the proper solvent to give **4** as pale brown crystals. IR (cm^{-1}): 2230 (CN), 1660 (CO). ^1H NMR (DMSO-d_6)δ: 6.9–8.1 (m, 16H, Ar-H + CH thiazole), 8.4 (s, 1H, CH-pyrazole).

7-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-2,3-dihydro-6-cyanothiazolo[3,2-a]pyrimidin-3,5-dione (5)

A mixture of **2** (0.01 mol), chloroacetic acid (0.01 mol), and fused sodium acetate (2 g) in a mixture of acetic acid/acetic anhydride (40 mL, 1:1) was heated under reflux for 6 h and left to cool. The reaction mixture was then diluted with water, shaken well, and allowed to stand 1 h. The

solid product was filtered off and recrystallized from the proper solvent to give **5** as yellow crystals. IR (cm^{-1}): 2220 (CN), 1720 (CO), 1680 (CO). ^1H NMR(DMSO-d_6)δ: 7.1–7.9 (m, 10H, Ar-H), 3.7 (s, 2H, CH_2), 8.4 (s, 1H, CH-pyrazole).

2-Benzylidene-7-(1,3-diphenyl-1*H*-pyrazol-4-yl)-2,3-dihydro-6-cyanothiazolo-[3,2-a]pyrimidin-3,5-dione (6)

Method A

A mixture of **2** (0.005 mol), chloroacetic acid (0.008 mol), benzaldehyde (0.005 mol), and fused sodium acetate (2.0 g) in a mixture of acetic acid/acetic anhydride (30 mL, 1:1) was heated under reflux for 4 h and left to cool. The reaction mixture was diluted with water. The solid was filtered off and crystallized from the proper solvent to give **6** as orange crystals. IR (cm^{-1}): 2230 (CN), 1700 (CO), 1680 (CO). ^1H NMR (DMSO-d_6)δ: 6.9–7.8 (m, 15H, Ar-H), 8.0 (s, 1H, CH=C), 8.4 (s, 1H, CH-pyrazole).

Method B

To a mixture of **5** (0.001 mol) and benzaldehyde (0.001 mol) in absolute ethanol (20 mL) was added piperidine (5 drops). The mixture was heated under reflux for 2 h. The crystalline product thus obtained after cooling was collected and recrystallized from the proper solvent to give 6 as orange crystals.

Compound **6** prepared by methods A and B have the same m.p. and mixed m.p.

6-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-2(3-pentan-2,4-dione)thio-5-cyanopyrimidin-4(3*H*)-one (7)

A mixture of **2** (0.01 mol) and potassium hydroxide (0.012 mol) in ethanol (30 mL) was stirred for 5 min, and then chloroacetylacetone (0.01 mol) was added dropwise while stirring for 2 h. The precipitate was filtered off, washed several times with water, and crystallized from the proper solvent to give 7 as orange crystals. IR (cm^{-1}): 3130 (NH), 2210 (CN), 1670 (2CO), 1650 (CO). ^1H NMR (DMSO-d_6) δ: 2.35 (s, 6H, $2COCH_3$), 6.9–7.8 (m, 11H, Ar-H + S-CH), 8.2 (s, 1H, CH-pyrazole), 9.2 (s, 1H, NH).

7-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-2-acetyl-3-methyl-6-cyanothiazolo[3,2-a]pyrimidin-5-one (8)

A mixture of **7** (0.001 mol) and acetic anhydride (10 mL) and pyridine (10 mL) was heated on a water bath for 6 h, cooled, and poured into ice

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cold water. The precipitate that formed was collected by filtration and recrystallized from the proper solvent to give 8 as brown crystals. IR (cm^{-1}): 2220 (CN), 1680 (CO), 1650 (CO). ^1H NMR (DMSO-d_6)δ: 2.65 (s, 3H, CH_3), 3.35 (s, 3H, $COCH_3$), 7.2–7.8 (m, 10H, Ar-H), 8.2 (s, 1H, CH-pyrazole).

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6-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-5-cyano-2-hydrazinopyrimidin-4(3*H*)-one (9)

Method A

A mixture of **2** (0.001 mol) and hydrazine hydrate (5 mL) was heated under reflux in pyridine (30 mL) for 6 h and then left to cool. The solid product was filtered off and recrystallized from the proper solvent to give **9** as buff crystals. IR (cm^{-1}): 3280–3200 (2NH + NH_2), 2230 (CN), 1660 (CO). ^1H NMR (DMSO-d_6)δ: 3.9 (s, 1H, NH_2), 7.2–7.8 (m, 10H, Ar-H), 8.2 (s, 1H, CH-pyrazole), 9.0 (s, 2H, 2NH).

Method B

A mixture of **3a** (0.001 mol) and hydrazine hydrate (7 mL) in absolute ethanol (20 mL) was refluxed for 10 h. The reaction mixture was poured onto ice. The product was isolated and crystallized from the proper solvent to give **9** as buff colored crystals. Compound **9** prepared by Methods A and B have the identical m.p. and mixed m.p.

6-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-5-cyano-2-azidopyrimidin-4(3*H*)-one (10)

A cold solution of sodium nitrite (2 g) in water (10 mL) was added to an ice bath solution of **9** (0.001 mol) in acetic acid (20 ml) with stirring. After the completion of the addition (30 min), the ice bath was removed, and stirring was continued for 1 h. The solid product was filtered off and recrystallized from the proper solvent to give **10** as yellow crystals. IR (cm^{-1}): 3450 (NH), 3369, 3120 (NH + NH_2), 2210 (CN), 2180 (N_3), 1660 (CO).^1H NMR (DMSO-d_6) δ: 7.4–7.9 (m, 10H, Ar-H), 8.2 (s, 1H, CH-pyrazole), 9.0 (s, 1H, NH). MS: m/z 380.19 (M^+, 15.35%).

6-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-2-(3,5-dimethylpyrazol-1-yl)-5-cyanopyrimidin-4(3*H*)-one (11)

A mixture of **9** (0.001 mol), acetylacetone (0.001 mol), and a few drops of acetic acid in ethanol (15 mL) was heated under reflux for 4 h, concentrated, and allowed to cool. The precipitate that formed was collected and recrystallized from the proper solvent to give **11** as yellow crystals.

IR (cm^{-1}): 3210 (NH), 2215 (CN), 1670 (CO). ^1H NMR (DMSO-d_6)δ: 2.9 (s, 3H, CH_3), 3.1 (s, 3H, CH_3), 7.2–7.8 (m, 10H, Ar-H), 8.2 (s, 1H, CH-pyrazole), 8.4 (s, 1H, CH-pyrazole), 9.1 (s, 1H, NH).

7-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-6-cyano-1,2,4-triazolo[4,3-*a*]pyrimidin-5(8*H*)-one (12)

A mixture of **9** (0.002 mol) and triethyl orthoformate (15 mL) was heated under reflux for 3 h. The precipitate that formed during heating was collected and recrystallized from the proper solvent to give **13** as pale yellow needles. IR (cm^{-1}): 3120 (NH), 2200 (CN), 1660 (CO). ^1H NMR (DMSO-d_6)δ: 4.8 (s, 1H, NH), 7.3–7.8 (m, 10H, Ar-H), 8.5 (s, 1H, CH-pyrazole), 8.9 (s, 1H, CH-triazole).

7-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-6-cyano-3-methyl-1,2,4-triazolo[4,3-*a*]pyrimi-din-5(8*H*)-one (13)

A mixture of **9** (0.001 mol) and acetic anhydride (15 mL) was heated under reflux for 6 h, and then allowed to cool, and poured onto ice cold water. The precipitate that formed was collected, washed with water, and recrystallized from the proper solvent to give 12 as shining yellow crystals. IR (cm^{-1}): 3130 (NH), 2210 (CN), 1660 (CO). ^1H NMR (DMSO-d_6) δ: 2.6 (s, 3H, CH_3), 4.4 (s, 1H, NH), 7.2–7.8 (m, 10H, Ar-H), 8.2 (s, 1H, CH-pyrazole).

7-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-3-thioxo-2,3-dihydro-6-cyano-1,2,4-triazolo[4,3-*a*]pyrimidin-5(8*H*)-one (14)

A mixture of **9** (0.002 mol) and carbon disulfide (2 mL) in dry pyridine (15 mL) was heated under reflux on a steam bath for 12 h. The solid product that separated after cooling was collected and recrystallized from the proper solvent to give **14** as orange needles. IR (cm^{-1}): 3200–3180 (2NH), 2210 (CN), 1670 (CO). ^1H NMR (TFA) δ: 7.3–7.8 (m, 10H, Ar-H), 8.7 (s, 1H, CH-pyrazole). MS: m/z 409.27 (M^+-2, 10.15%).

The Alkylation of 14: The Formation of Thioethers (15a–c)

A mixture of **14** (0.001 mol), the appropriate halo compounds (0.01 mol), and 10% aqueous KOH (5.6 mL, 0.01 mol) in dimethyl formamide (25 mL) was stirred at r.t. for 2 h and then diluted with water. The precipitate formed was filtered off, was washed with water, dried, and recrystallized from the proper solvent to give **15a–c**.

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7-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-3-ethylthio-2,3-dihydro-6-cyano-1,2,4-triazolo[4,3-*a*]pyrimidin-5(8*H*)-one (15a)

Yellowish crystals. IR (cm^{-1}): 3210 (NH), 2210 (CN), 1650 (CO). ^{1}H NMR (DMSO-d_6)δ: 1.2–1.4 (t, 3H, CH_3), 3.5–3.7 (q, 2H, CH_2), 7.2–7.7 (m, 10H, Ar-H), 8.4 (s, 1H, CH-pyrazole), 9.2 (s, 1H, NH).

7-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-3-methylbenzylthio-2,3-dihydro-6-cyano-1,2,4-triazolo[4,3-a]pyrimidin-5(8*H*)-one (15b)

Yellowish crystals. IR (cm^{-1}): 3220 (NH), 2215 (CN), 1680 (CO), 1660 (CO). ^{1}H NMR (DMSO-d_6)δ: 4.4 (s, 2H, CH_2), 6.9–7.7 (m, 15H, Ar-H), 8.3 (s, 1H, CH-pyrazole), 9.3 (s, 1H, NH).

Ethyl [7-(1,3-diphenyl-1*H*-pyrazol-4-yl)-2,3-dihydro-6-cyano-1,2,4-triazolo[4,3-*a*]pyrimidinthio] acetate-5(8*H*)-one (15c)

Yellowish crystals. IR (cm^{-1}): 3220 (NH), 2215 (CN), 1735 (CO), 1660 (CO). ^{1}H NMR (DMSO-d_6)δ: 1.3–1.5 (t, 3H, $CO_2CH_2CH_3$), 3.9–4.2 (q, 2H, $CO_2CH_2CH_3$), 4.6 (s, 2H, CH_2), 7.3–7.7 (m, 10H, Ar-H), 8.3 (s, 1H, CH-pyrazole), 9.3 (s, 1H, NH).

6-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-5-cyano-3-ethyl-4-oxo-1,2,3,4-tetrahydropyrimidine-2-ethylthio (16)

A mixture of **2** (0.005 mol), ethyl iodide (0.015 mol), and anhydrous sodium acetate (2 g) in ethanol (30 mL) was heated under reflux for 6 h, and then left to cool. The product that formed was filtered off and recrystallized from the proper solvent to give **16** as pale yellow crystals. IR (cm^{-1}): 2220 (CN), 1650 (CO). ^{1}H NMR (DMSO-d_6) δ: 0.98-1.2 (t, 3H, N-CH_2CH_3), 1.2–1.4 (t, 3H, S-CH_2CH_3), 2.9–3.2 (q, 2H, N-CH_2CH_3), 3.5–3.8 (q, 2H, S-CH_2CH_3), 7.2–7.8 (m, 10H, Ar-H), 8.5 (s, 1H, CH-pyrazole). MS: m/z 427 (M^+, 10.25%).

6-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-2-hydrazino-5-cyano-3-ethyl-4-oxo-1,2,3,4-tetrahydropyrimidine (17)

A mixture of **16** (0.001 mol) and hydrazine hydrate (1 mL) in absolute ethanol (15 mL) was heated under reflux for 10 h .and then poured onto ice. The product that formed was collected by filtration and crystallized from the proper solvent to give **17** as yellow crystals. IR (cm^{-1}): 3330–3250 (NH + NH_2), 2220 (CN), 1650 (CO). ^{1}H NMR (DMSO-d_6)δ:

0.98–1.2 (t, 3H, N-CH_2CH_3), 2.8–3.0 (q, 2H, N-CH_2CH_3), 3.9 (s, 2H, NH_2), 7.3–7.8 (m, 10H, Ar-H), 8.3 (s, 1H, CH-pyrazole), 9.2 (s, 1H, NH).

7-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-6-cyano-4-ethyl-5-oxo-[1,2,3,4]-tetrazolopyrimid-ine (18)

A solution of sodium nitrite (0.005 mol) in the least amount of water was added dropwise to an ice-cold solution of **17** (0.002 mol) in a mixture of acetic acid (10 mL) and hydrochloric acid (5 mL), keeping an ice bath at 0–5°C. The reaction mixture was allowed to stand overnight at r.t., then it was poured into water. The solid product obtained was filtered off and recrystallized from the proper solvent to give **18** as pale brown needles. IR (cm^{-1}): 2215 (CN), 1660 (CO). ^{1}H NMR (DMSO-d_6)δ: 1.1-1.2 (t, 3H, N—CH_2CH_3), 2.9–3.2 (q, 2H, N—CH_2CH_3), 7.4–7.9 (m, 10H, Ar-H), 8.5 (s, 1H, CH-pyrazole). MS: m/z 408 (M^+, 21.09%).

7-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-1-mercapto-6-cyano-4-ethyl-5-oxo-[1,2,4]tria zoloyrimidine (19)

A mixture of **17** (0.002 mol) and excess carbon disulphide (5.5 mL) in ethanolic sodium hydroxide solution (0.01 mol in 20 mL of ethanol) was heated under reflux at 80°C on steam bath for 12 h. The reaction mixture was allowed to cool to r.t., poured into water, and neutralized by diluted acetic acid. The solid product obtained was filtered off, dried and crystallized from the proper solvent to give **19** as orange crystals. IR (cm^{-1}): 2215 (CN), 1675 (CO). ^{1}H NMR (DMSO-d_6) δ: 1.2-1.4 (t, 3H, N—CH_2CH_3), 2.8–3.1 (q, 2H, N—CH_2CH_3), 7.2–7.8 (m, 10H, Ar-H), 8.5 (s, 1H, CH-pyrazole).

6-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-2-(3-amino-pyrazol-5(4*H*)-one-1-yl)-3-ethyl-5-cyaanopyrimidin-4(3*H*)-one (20)

A mixture of **17** (0.01 mol), ethyl cyanoacetate (0.01 mol), and sodium ethoxide (0.01 mol) in absolute ethanol (20 mL) was stirred at a reflux temperature for 8 h and then allowed to cool to r.t., poured into cold water, and neutralized by diluted acetic acid. The solid product obtained was filtered off, dried, and crystallized from the proper solvent to give **20** as orange crystals. IR (cm^{-1}): 3360, 3290 (NH_2), 2220 (CN), 1695 (CO), 1675 (CO). ^{1}H NMR (DMSO-d_6) δ: 1.1–1.3 (t, 3H, N-CH_2CH_3), 2.9–3.1 (q, 2H, N-CH_2CH_3), 3.5 (s, 2H, CH_2-pyrazole), 7.4–7.8 (m, 10H, Ar-H), 8.4 (s, 1H, CH-pyrazole), 10.3 (br, 2H, NH_2, D_2O-exchangeable).

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6-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-2-(3-methyl-pyrazol-5(4*H*)-one-1-yl)-3-ethyl-5-cyanopyrimidin-4(3*H*)-one (21)

A mixture of **17** (0.001 mol) and ethyl acetoacetate (0.001 mol) in absolute ethanol (30 mL) was stirred at a reflux temperature for 20 h. The reaction mixture was allowed to cool to r.t. and then poured into cold water. The precipitate that formed was filtered off, dried, and crystallized from the proper solvent to give **21** as orange crystals. IR (cm^{-1}): 2215 (CN), 1685 (CO), 1665 (CO). ^{1}H NMR (DMSO-d_6) δ: 1.3–1.5 (t, 3H, N-CH_2CH_3), 2.3 (s, 3H, CH_3), 2.9-3.1 (q, 2H, N-CH_2CH_3), 4.6 (s, 2H, CH_2-pyrazole), 7.4–7.8 (m, 10H, Ar-H), 8.5 (s, 1H, CH-pyrazole).

9-Ethyl-6-(1,3-diphenyl-1*H*-pyrazol-4-yl)-8-oxo-4-phenyl-2*H*-pyrimido[2,1-*c*] [1,2,4]triazin-7-carbonitrile (22)

A mixture of **17** (0.002 mol) and phenacyl bromide (0.002 mol) in dry xylene (30 mL) was heated under reflux for 5 h. The solid that separated upon cooling was filtered off and crystallized from the proper solvent to give **22** as yellowish crystals. IR (cm^{-1}): 3400 (NH), 2215 (CN), 1660 (CO). ^{1}H NMR (DMSO-d_6)δ: 1.3–1.5 (t, 3H, N-CH_2CH_3), 2.9–3.1 (q, 2H, N-CH_2CH_3), 7.3–8.1 (m, 15H, Ar-H), 8.4 (s, 1H, CH-pyrazole), 9.2 (s, 1H, CH- triazine), 10.3 (s, 1H, NH-triazine).

ANTIMICROBIAL ACTIVITY

Ten compounds were screened in vitro for their antimicrobial activities against two strains of bacteria (*Bacillus cereus*, *Escherichia coli*), two strains of fungi (*Botrytis, and Geotrichum candidum*) and one strain of yeast (*Candida albicans*) using the paper disc method.[31] The screened compounds were dissolved in DMSO to get a solution of 1% concentration. Filtered paper discs (Whatman No. 1 filter paper, 5 mm diameter) were saturated with this solution. The discs were placed on the surface of solidified nutrient agar dishes seeded by the tested bacteria or Czapek's Dox agar dishes seeded by the tested fingi. Inhibition zones were measured at the end of an incubation period of 48 h (at 37 ^{o}C for bacteria and at 28^{o}C for fungi). Tioconazole (Tyrosyd^R) was used as a reference substance.

The results revealed that all tested compounds exhibit moderate to strong activity against *E. coli* and were inactive against *B. cereus*. However, only compounds **4**, **6**, **8**, **14**, and **20** showed considerable potency against two fungal species used. None of the tested compounds were active against *C. albicans* (Table II).

TABLE II Antibacterial and Antifungal Activities of Some New Pyrazole Derivatives*

Compound	*B. cereus*	*E. coli*	*Botrytis*	*G. candidum*	*C. albicans*
2	—**	14	7	—	—
4	—	23	—	12	—
6	—	20	10	16	—
8	—	31	20	10	—
11	—	9	6	—	—
14	—	26	30	14	—
15a	—	10	—	9	—
19	—	30	—	—	—
20	—	17	12	—	—
22	—	28	—	—	—
Tioconazole (Tyrosyd^R)	25	32	33	18	41

The activity is expressed as diameter of the inhibition zone (mm).
**No inhibition zone = —.
*This antibacterial and antifungal screening has been done in the Mycological Center, Faculty of Science, Assiut University, Egypt.

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