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Phosphorus, Sulfur, and Silicon and the Related Elements

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Synthesis of Some New Biologically Active Sulfur Compounds Containing Pyrazolo[3,4-d] pyrimidine Moiety

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SYNTHESIS OF SOME NEW BIOLOGICALLY ACTIVE SULFUR COMPOUNDS CONTAINING PYRAZOLO[3,4-d] PYRIMIDINE MOIETY

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(Received January 8, 2003; accepted March 14, 2003)

A novel series of the pyrazolo[3,4-d]pyrimidines having biologically active sulfur moieties **3-20** were prepared via reaction of 4-mercapto-1phenyl-1H-pyrazolo[3,4-d]pyrimidine **3** with different reagents. Identification of the new compounds was established by elemental analyses, IR, ¹H-NMR, and mass spectral data. Some of the obtained compounds showed the interesting antimicrobial activity comparable to antibiotic chloramphenicol as standard antibacterial agent and Terbinafin as a standard antifungal agent.

Keywords: Sulfur containing pyrazolo[3,4-d]pyrimidine and antimicrobial activity

Pyrazolo[3,4-d]pyrimidines are of considerable chemical and pharmacological importance as purine analoges.^{1–3} Various compounds with related structures also possess antimicrobial,⁴ antitumor, and antileukemia^{5,6} activities. It is reported that many sulfur containing compounds have a biologically active agents.^{7–12} As a continuation of our work on azoloazines,⁴ we aimed to incorporate the sulfur moiety into the 4-position of the pyrazolo[3,4-d]pyrimidine ring system to thus obtain a new sulfur heterocyclic system which is expected to possess notable chemical and biological activities.

Many thanks are due to Prof. Dr. A. I. El-Batal in the Department of Drug Radiation Research, National Centre for Radiation Research and Technology for performing the antimicrobial activity of the synthesized compounds.

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SCHEME 1

INVESTIGATIONS, RESULTS AND DISCUSSION

Chemistry

The synthetic strategy to synthesize the target sulfur compounds **3-20** is depicted in Schemes 1 and 2. The starting material



SCHEME 2

1-phenyl-1,5-dihydropyrazolo[3,4-d]pyrimidine 1^{13} was treated with phosphorus penta sulfide to afford the 4-mercapto-1-phenyl-1*H*-pyrazolo[3,4-d]pyrimidine **3**. Compound **3** also was obtained in quantitative yield via reaction of chloro compound 2^{14} with thiourea in ethanol. IR spectrum of compound **3** showed the absence of (C=O) band and presence bands at 3390 cm⁻¹ (NH), 3100 cm⁻¹ (CH arom.), 1600 cm⁻¹ (C=N), 1188 cm⁻¹ (C=S). ¹H-NMR spectrum of compound (**3**, in DMSO-d₆) revealed signals at 7.0-7.8 (m, 5H, Ar-H), 8.2, 8.4 (2s, 2H, CH pyrazole + CH pyrimidine), 9.2 (s, 1H, NH) (Scheme 1).

The 4-mercapto function **3** was alkylated using variety of alkyl halide such as chloroacetone and ethyl bromoacetate to give the alkylthio derivatives **4** and **6**. In addition compound **3** was reacted with chloroacetic acid to yield the corresponding 4-thioacetic acid derivative **5**. IR spectrum of compound **4** exhibited bands at 2924 cm⁻¹ (CH aliph.), 1728 cm⁻¹ (C=O). ¹H-NMR spectrum of compound (**4** in CDCl₃) showed signals at 2.6 (s, 3H, COCH₃), 4.4 (s, 2H, SCH₂CO), 7.2-8.0 (m, 5H, Ar-H), 8.3, 8.8 (2s, 2H, CH pyrazole + CH pyrimidine). IR spectrum of compound **6** revealed bands at 2935 cm⁻¹ (CH aliph.), 1735 cm⁻¹ (C=O). ¹H-NMR spectrum of compound (**6** in DMSO-d₆) exhibited signals at 1.2 (t, 3H, CH₃ ester), 4.2 (q, 2H, CH₂ ester), 4.4 (s, 2H, SCH₂CO), 7.5-8.2 (m, 5H, Ar-H), 8.7, 8.9 (2s, 2H, CH pyrazole + CH pyrimidine). IR spectrum of compound **5** exhibited bands at 3417 cm⁻¹ (OH), 3100 cm⁻¹ (CH arom.), 2931 cm⁻¹ (CH aliph.), 1728 cm⁻¹ (C=O), 1643 cm⁻¹ (C=N).

Interaction of compound **6** with 2-aminoethanol afforded the corresponding pyrazolopyrimidine derivative **7**; its IR spectrum showed bands at 3448 cm⁻¹ (OH), 3139 cm⁻¹ (NH), 2924 cm⁻¹ (CH aliph.), 1597 cm⁻¹ (C=N). Mass spectrum of compound **7** showed a molecular ion peak m/z 329 (M⁺, 0.86%) with a base peak at 228 (100%), and other significant peaks appeared at 269 (5.80%), 229 (17.51%), 168 (8.84%), 142 (5.81%), 91 (5.13%), 77 (23.02%).

The strategic starting material 4-[(1-phenyl-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)thio]acetylhydrazide **8** was obtained in good yield via reaction of the corresponding ester derivative **6** with hydrazine hydrate in refluxing ethanol. IR spectrum of **8** exhibited bands at 3336, 3209 cm⁻¹ (NH,NH₂), 2935 cm⁻¹ (CH aliph.), 1655 cm⁻¹ (C=O), 1593 cm⁻¹ (C=N). ¹H-NMR spectrum of compound (**8** in DMSO-d₆) revealed signals at 4.8 (s, 2H, CH₂CO), 7.3-8.2 (m, 7H, Ar-H + NH₂), 8.4, 8.6 (2s, 2H, CH pyrazole + CH pyrimidine), 10.6 (s, 1H, NH).

Interaction of compound 8 with ethyl-2-cyano-3-ethoxyacrylate in methanol containing few drops of acetic acid yielded the pyrazole derivative 9. IR spectrum showed bands at 3425, 3302 cm⁻¹ (NH₂), 1689, 1680 cm⁻¹ (2C=O), 1589 cm⁻¹ (C=N). ¹H-NMR spectrum of compound (9 in CDCl₃) revealed signals at 1.3 (t, 3H, CH₃ ester), 4.3 (q, 2H, CH₂ ester), 4.8 (s, 2H, CH₂CO), 7.1-8.2 (m, 7H, Ar-H + NH₂), 8.3, 8.8, 8.9 (3s, 3H, CH pyrazole + CH pyrazoline + CH pyrimidine).

Refluxing of compound **8** in acetic anhydride furnished the corresponding monoacetyl derivative **10**. IR spectrum of compound **10** revealed bands at 3140 cm⁻¹ (NH), 2931 cm⁻¹ (CH aliph.), 1728 cm⁻¹ (C=O), 1590 cm⁻¹ (C=N). ¹H-NMR spectrum of compound (**10** in CDCl₃) exhibited signals at 2.6 (s, 3H, COCH₃), 4.2 (s, 2H, CH₂CO), 7.2-8.1 (m, 5H, Ar-H), 8.3, 8.8 (2s, 2H, CH pyrazole + CH pyrimidine), 8.5, 9.4 (2s, 2H, 2NH).

On the other hand interaction of compound **3** with benzylaminocarbonylmethyl chloride in dimethylformamide yielded the corresponding 4-(benzylaminocarbonylmethylthio)pyrazolo[3,4-d]pyrimidine derivative **11**. IR spectrum showed bands at 3278 cm^{-1} (NH), 3062 cm^{-1} (CH arom.), 2924 cm⁻¹ (CH aliph.), 1643 cm⁻¹ (C=O). ¹H-NMR spectrum of compound (**11** in CDCl₃) showed signals at 4.2 (s, 2H, CH₂-Ph), 4.5 (s, 2H, CH₂CO), 7.1-8.1 (m, 10H, Ar-H), 8.4, 8.8 (2s, 2H, CH pyrazole + CH pyrimidine), 9.2 (s, 1H, NH).

Also, reaction of compound **3** with substituted sulfamoylphenylaminocarbonylmethyl chloride in dimethylformamide furnished the corresponding 4-(substituted sulfamoylphenylaminocarbonylmethylthio)-pyrazolo[3,4-d]pyrimidine **12-14** respectively (Scheme 2). IR spectrum of compounds **12-14** revealed the presence of (NH) at 3260-3180 cm⁻¹ and (C=O) band at 1700–1680 cm⁻¹. Mass spectrum of compound **12** showed a molecular ion peak m/z 520 (M-1, 1.14%), 519 (M-2, 0.94%) with a base peak at 228 (100%), and other significant peaks appeared at 404 (5.83%), 385 (33.91%), 286 (3.51%), 195 (56.87%), 156 (57.74%), 77 (70.53%).

In addition 4-[N-(substitutedphenyl)carbamoylmethylthio)]pyrazolo[3,4-d]pyrimidines **15-16** were obtained via reaction of compound **3** with 2'-chloro-4-substituted-acetanilide. IR spectrum of compound **15** showed bands at 3317 cm⁻¹ (NH), 2923 cm⁻¹ (CH aliph.), 1658 cm⁻¹ (C=O). IR spectrum of compound **16** revealed bands at 3309 cm⁻¹ (NH), 1658 cm⁻¹ (C=O). ¹H-NMR spectrum of compound (**15** in DMSO-d₆) exhibited signals at 2.2 (s, 3H, CH₃), 4.3 (s, 2H, CH₂CO), 7.1-8.1 (m, 9H, Ar-H), 8.6, 8.8 (2s, 2H, CH pyrazole + CH pyrimidine), 10.4 (s, 1H, NH). IR spectrum of compound **17** showed bands at 3448 cm⁻¹ (NH), 2916 cm⁻¹ (CH aliph.), 1689 cm⁻¹ (C=O), 1566 cm⁻¹ (C=N). Mass spectrum of compound **17** exhibited a molecular ion peak m/z 368 (M⁺, 0.12%), with a base peak at 269 (100%) and other significant peaks appeared at 336 (0.32%), 250 (0.81%), 195 (12.32%), 168 (8.30%), 127 (15.13%), 77 (17.81%).

Finally, interaction of compound **3** with chloroacetonitrile, benzyl chloride, and/or phenacylbromide gave the corresponding 4-thiomethyl derivatives **18–20** respectively. IR spectrum of compound **18** showed bands at 3070 cm⁻¹ (CH arom.), 2985 cm⁻¹ (CH aliph.), 2245 cm⁻¹ (C=N), 1558 cm⁻¹ (C=N). IR spectrum of compound **19** showed bands at 3086 cm⁻¹ (CH arom.), 2923 cm⁻¹ (CH aliph.), 1550 cm⁻¹ (C=N). ¹H-NMR spectrum of compound (**19** in DMSO-d₆) revealed signals at 4.9 (s, 2H, CH₂), 7.1-8.2 (m, 10H, Ar-H), 8.4, 8.8 (2s, 2H, CH pyrazole + CH pyrimidine). IR spectrum of compound **20** revealed bands at 2923 cm⁻¹ (CH aliph.), 1689 cm⁻¹ (C=O), 1635 cm⁻¹ (C=N). ¹H-NMR spectrum of compound (**20** in DMSO-d₆) showed signals at 4.2 (s, 2H, CH₂CO), 7.1-8.1 (m, 10H, Ar-H), 8.3, 8.6 (2s, 2H, CH pyrazole + CH pyrimidine).

$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	a 1		37: 11		Analysi	s Require	d/(Found) %
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Compd. No.	m.p. (°C)	Yield (%)	Mol. Formula (mol. wt.)	С	Н	Ν
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	3	276–278	86	$C_{11}H_8N_4S$	57.89	3.51	24.56
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$				(228)	57.60	3.20	24.80
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	4	122 - 124	71	$C_{14}H_{12}N_4OS$	59.15	4.23	19.72
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$				(284)	58.80	4.40	19.50
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	5	303 - 305	68	$\mathrm{C_{13}H_{10}N_4O_2S}$	54.55	3.50	19.58
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$				(286)	54.80	3.60	19.20
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	6	90 - 92	84	$\mathrm{C_{15}H_{14}N_4O_2S}$	57.32	4.46	17.83
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$				(314)	57.60	4.20	17.50
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	7	292 - 294	77	$\mathrm{C_{15}H_{15}N_5O_2S}$	54.71	4.56	21.28
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$				(329)	54.40	4.20	21.50
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	8	190 - 192	91	$C_{13}H_{12}N_6OS$	52.00	4.00	28.00
$\begin{array}{cccccccccccccccccccccccccccccccccccc$				(300)	52.30	4.20	28.40
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	9	218 - 220	59	$C_{19}H_{17}N_7O_3S$	53.90	4.02	23.17
$\begin{array}{cccccccccccccccccccccccccccccccccccc$				(423)	53.60	4.30	23.50
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	10	113 - 115	62	$\mathrm{C_{15}H_{14}N_6O_2S}$	52.63	4.09	24.56
11 $206-208$ 69 $C_{20}H_{17}N_5OS$ 64.00 4.53 18.67				(342)	52.40	4.40	24.20
	11	206 - 208	69	$C_{20}H_{17}N_5OS$	64.00	4.53	18.67
(375) 64.20 4.30 18.30				(375)	64.20	4.30	18.30
12 220–222 75 $C_{23}H_{19}N_7O_4S_2$ 52.98 3.65 18.81	12	220 - 222	75	$C_{23}H_{19}N_7O_4S_2$	52.98	3.65	18.81
(521) 52.70 3.90 18.50	10	222 242		(521)	52.70	3.90	18.50
13 238–240 61 $C_{25}H_{22}N_8O_3S_2$ 54.95 4.03 20.51	13	238 - 240	61	$C_{25}H_{22}N_8O_3S_2$	54.95	4.03	20.51
(546) 54.60 4.30 20.80		222 222		(546)	54.60	4.30	20.80
$14 226-228 68 C_{22}H_{18}N_8O_4S_3 47.65 3.25 20.22 (51)$	14	226 - 228	68	$C_{22}H_{18}N_8O_4S_3$	47.65	3.25	20.22
(554) 47.30 3.50 19.90		105 105	50	(554)	47.30	3.50	19.90
15 195–197 56 $C_{20}H_{17}N_5OS$ 64.00 4.53 18.67	15	195–197	56	$C_{20}H_{17}N_50S$	64.00	4.53	18.67
(375) 64.30 4.70 18.40	10	000 011	C O	(375) C H N OCCI	64.30	4.70	18.40
16 $209-211$ 68 $C_{19}H_{14}N_5OSCI$ 57.65 3.54 17.70 (205.5) 57.40 2.90 17.40	16	209–211	68	(205.5)	57.65	3.54	17.70
(395.5) 57.40 3.80 17.40	17	014 010	79	(390.0) C II N OS	57.40 59.17	3.80	17.40
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	17	214-216	13	(269)	52.17	3.20	22.83
(306) 32.00 3.00 22.00 10 146 149 66 (CHNS 5949 9.97 96.99	10	146 149	<u>cc</u>	(308) C H N S	52.50 59.49	3.3U 9.97	22.60
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	10	140-148	00	(967)	00.40 59 10	0.07 2.60	20.22
$(207) 00.10 3.00 20.00 10 111 112 62 C_{11} H_{11} N S 67.02 4.40 17.61 $	10	111 119	69	(207) C. H. N.S	00.1U 67.09	3.00 4.40	20.00
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	19	111-113	02	(218)	67 70	4.40	17.01
(310) 07.70 4.20 17.30 90 157 150 76 CH. N.OS 65.00 4.05 16.19	20	157 150	76	(010) CarHanNaOS	65.00	4.20	16.18
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	40	107-109	10	(346)	65.60	4.00	16 50

TABLE I Physical and Analytical Data of the Synthesized Compounds

Antimicrobial Activity

The antimicrobial screening of the synthesized compounds was undertaken using the diffusion agar technique.¹⁵ Table II lists the screening results of the tested compounds against the Gram-positive bacteria *Staphylococcus aureus*, *Bacillus subtilis* and the Gram-negative

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Compd. No.	5	2.5 mg/ml		5 11	2.5 ng/ml	-	5 m	2.5] g/ml		5 S	2.5 /ml		5 5 mg	2.5 ¢/ml	1	5 D	2.5 Ig/ml	ч	2 D	2.5 g/ml	H	22 11	2.5 g/ml	-
3	0	0	0	0	0	0	0	0	_	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
8	+ +	++	+	+	0	0	+	0	_	+	0	0	+	0	0	+	0	0	0	0	0	0	0	0
12	+	+	+	0	0	0	0	0	_	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
17	0	0	0	0	0	0	0	0	<u>т</u>	0	0	+	0	0	0	0	0	0	0	0	0	0	0	0
19	0	0	0	0	0	0	0	0	_	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
20	0	0	0	0	0	0	0	0	_	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Chloramphenicol	+ +	+ +	++	++	++	++	+++	+++++	++	+++	+++++++++++++++++++++++++++++++++++++++	÷	0	0	0	0	0	0	0	0	0	0	0	0
Terbinafin	0	0	0	0	0	0	0	0	_	0	0	+ 0	+++++++++++++++++++++++++++++++++++++++	+	++++	++	++++++	+	+++	+++++++++++++++++++++++++++++++++++++++	++	+++++++++++++++++++++++++++++++++++++++	+++	+
DMF	Ι	Ι	Ι	Ι	Ι	Ι	Ι	' I		I	I	I	I	Ι	Ι	Ι	Ι	Ι	Ι	I	I	I	Ι	Ι
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Inhibition values = 0.1-0.5 cm beyond control = +; Inhibition values = 0.6-1.0 cm beyond control = ++; Inhibition values = 1.1-1.5 cm

beyond control = + + +; 0 =not detected.

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bacteria, *Pseudomonas aeruginosa*, *Escherichia coli*. In addition to the pathogenic fungi *Aspergillus fumigatus*, *Penicillium italicum*, *Candida albicans*, and *Syncephalastrum racemosum*. The reference antibiotic chloramphenicol and fungicide Terbinafin were used as a positive controles for comparison. The fungi cultures were maintained on Czapek's Dox agar medium. The tested compounds were dissolved in N, N-dimethylformamide (DMF), which showed no inhibition zones.

The results are illustrated in Table II. The antibacterial activity of the synthesized compounds showed that the pyrazolopyrimidine having hydrazide moiety **8** was found to be the most active compound against Gram-positive bacteria (*Staphylococcus aureus*). Also, compound **8** showed a moderate activity against *Bacillus subtilis*, *Aspergillus fumigatus*, and *Penicillium italicum*. On the other hand compounds **8** and **17** exhibited a moderate activity against Gram-negative bacteria *Pseudomonas aeruginosa* and *Escherichia coli*. In addition compound **12** having methoxazole moiety exhibited a modarate activity against Gram positive bacteria *Staphylococcus aureus*.

These results indicated that the biologically active compound **8** was almost as potent as the standard antibiotic chloramphenicol as positive control.

EXPERIMENTAL

Apparatus and Methods

All m.p.s are uncorrected. Elemental analyses were carried out at the microanalytical laboratories of the Faculty of Science, Cairo University. The IR spectra (KBr) were measured on a Shimadzu IR 110 spectrophotometer, ¹H-NMR spectra were obtained on a BRUKER proton NMR-Avance 300 (300, MHz), in DMSO-d₆ and CDCl₃ as a solvent, using tetramethylsilane (TMS) as internal standard. Mass spectra were run on HP Model MS-5988.

Synthesis of 4-Mercapto-1-phenyl-1,5-dihydro-1*H*pyrazolo[3,4-d]pyrimidine 3

Method A

A mixture of compound 1 (0.01 mmol), and P_2S_5 (5 g) in pyridine (50 ml) was heated under reflux for 10 h. The solvent was removed under reduced pressure and the obtained residue was washed with dil. HCl, and recrystallized from dioxane to give 3 (Table I).

Method B

A mixture of compound $\mathbf{2}$ (0.01 mmol) and thiourea (0.015 mmol) in ethanol was refluxed for 7 h. The obtained solid was recrystallized from ethanol to give $\mathbf{2}$ (m.p. and m.m.p.).

Formation of 4-(Methylcarbonylmethylthio)-1-phenyl-1*H*-pyrazolo[3,4-d]pyrimidine 4 and 4-Thioacetic Acid-1-phenyl-1*H*-pyrazolo[3,4-d]pyrimidine 5 and 4-Ethoxycarbonylmethyl)thio-1-phenyl-1*H*-pyrazolo-[3,4-d]pyrimidine 6

To a solution of compound **3** (0.01 mmol) in dry acetone (50 ml), anhydrous K_2CO_3 (2 g) was added followed by either chloroacetone, 2chloroacetic acid, or ethyl bromoacetate (0.015 mmol). The reaction mixture was heated under reflux for 24 h, filtered while hot, and the filtrate was concentrated in vacuo to give **4-6** respectively (Table I).

Synthesis of N-(2-Hydroxyethyl)-4-[(1-phenyl-1*H*pyrazolo[3,4-d]pyrimidin-4-yl)thio]acetamide 7

A solution of ester 6 (0.01 mmol) and 2-aminoethanol (0.02 mmol) in ethanol (50 ml) was heated under reflux for 3 h. The precipitated solid was filtered on hot, dried, and recrystallized from dioxane to give 7 (Table I).

Preparation of 4-[(1-Phenyl-1*H*-pyrazolo [3,4-d]pyrimidine-4-yl)thio]acetylhydrazine 8

A solution of the ester derivative $\mathbf{6}$ (0.01 mmol) and hydrazine hydrate (85%, 10 ml) in ethanol (50 ml) was heated under reflux for 3 h. The solvent was evaporated and the obtained residue was recrystallized from ethanol to give $\mathbf{8}$ (Table I).

Formation of 1-Phenyl-1*H*-4-[acetylthio-2-(5'-amino-4'carbethoxypyrazoline)-1-yl]pyrazolo[3,4-d]pyrimidine 9

A mixture of **8** (0.01 mmol) and ethyl-2-cyano-3-ethoxyacrylate (0.012 mmol) in methanol containing few drops of acetic acid was refluxed for 8 h. The obtained solid was recrystallized from ethanol to give **9** (Table I).

Synthesis of 4-[(1-phenyl-1*H*-pyrazolo[3,4-d]pyrimidin-4yl)-thio]acetoacetylhydrazine 10

To a solution of $\mathbf{8}$ (0.01 mmol) in acetic anhydride was refluxed for 1 h. The obtained solid was recrystallized from ethanol to give $\mathbf{10}$ (Table I).

Synthesis of 4-[(Benzylaminocarbonylmethyl-4yl)thio]methyl-1-phenyl-pyrazolo[3,4-d]pyrimidine 11

A mixture of $\mathbf{3}$ (0.01 mmol) and 2'-chloro-benzylacetanilide (0.012 mmol) in dimethylformamide (20 ml) was refluxed for 8 h. The obtained product was recrystallized from dioxane to give $\mathbf{11}$ (Table I).

Formation of 4-(Substituted Sulfamoylphenylaminocarbonylmethylthio)-1-phenylpyrazolo[3,4-d]pyrimidine 12-14

A mixture of compound **3** (0.01 mmol) and substituted sulfamoylphenylaminocarbonylmethyl chloride (0.012 mmol) in dimethylformamide (20 ml) was refluxed for 10 h. The obtained solid was recrystallized from DMF-ethanol to give **12-14** respectively (Table I).

Synthesis of 4-[N-(Substitutedphenyl)carbamoylmethylthio]-1-phenyl-1*H*-pyrazolo [3,4-d]pyrimidine 15-17

A mixture of **3** (0.01 mmol) and 2'-chloro-4-substituted acetanilide (0.012 mmol) in dimethylformamide (20 ml) was refluxed for 12 h. The obtained solid was recrystallized from acetic acid to give **15-17** respectively (Table I).

Synthesis of 4-Cyanomethylthio-1-phenyl-1*H*pyrazolo[3,4-d]-pyrimidine 18 and 4-Phenylmethylthio-1-phenyl-1*H*-pyrazolo-[3,4-d]pyrimidine 19

To a solution of $\mathbf{3}$ (0.01 mmol) in dry acetone (50 ml), anhydrous potassium carbonate (2 g) was added followed by either 2-chloroacetonitrile or benzyl chloride (0.015 mmol). The reaction mixture was heated under reflux for 20 h, filtered while hot, and the filterate was concentrated in vacuo to give the crude product which was recrystallized from ethanol to give **18** and **19** respectively (Table I).

Synthesis of 4-(Phenylcarbonylmethylthio)-1-phenyl-1*H*-pyrazolo[3,4-d]pyrimidine 20

A mixture of **3** (0.01 mmol), phenacylbromide (0.01 mmol), and anhydrous K_2CO_3 (2 g) in dry acetone (50 ml) was heated under reflux for 24 h. The reaction mixture was filtered while hot, and the filtrate was

concentrated under reduced pressure then cooled. The obtained solid was filtered, dried, and recrystallized from ethanol to give **20** (Table I).

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