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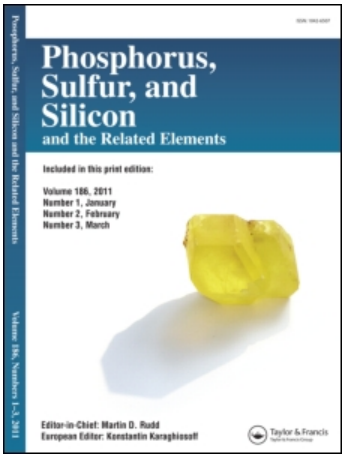


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# Synthesis of Some New Biologically Active Sulfur Compounds Containing Pyrazolo[3,4-d] pyrimidine Moiety

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Online publication date: 27 October 2010

**To cite this Article** Ismail, Zeinab H. , Abdel-Gawad, Soad M. , Abdel-Aziem, Anhar and Ghorab, M. M.(2003) 'Synthesis of Some New Biologically Active Sulfur Compounds Containing Pyrazolo[3,4-d] pyrimidine Moiety', Phosphorus, Sulfur, and Silicon and the Related Elements, 178: 8, 1795 — 1805
**To link to this Article: DOI:** 10.1080/10426500307825
**URL:** http://dx.doi.org/10.1080/10426500307825

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*Phosphorus, Sulfur, and Silicon*, 178:1795–1805, 2003
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ISSN: 1042-6507 print
DOI: 10.1080/10426500390221447

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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)

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*A novel series of the pyrazolo[3,4-d]pyrimidines having biologically active sulfur moieties* ***3-20*** *were prepared via reaction of 4-mercapto-1-phenyl-1*H*-pyrazolo[3,4-d]pyrimidine* ***3*** *with different reagents. Identification of the new compounds was established by elemental analyses, IR,* $^1$*H-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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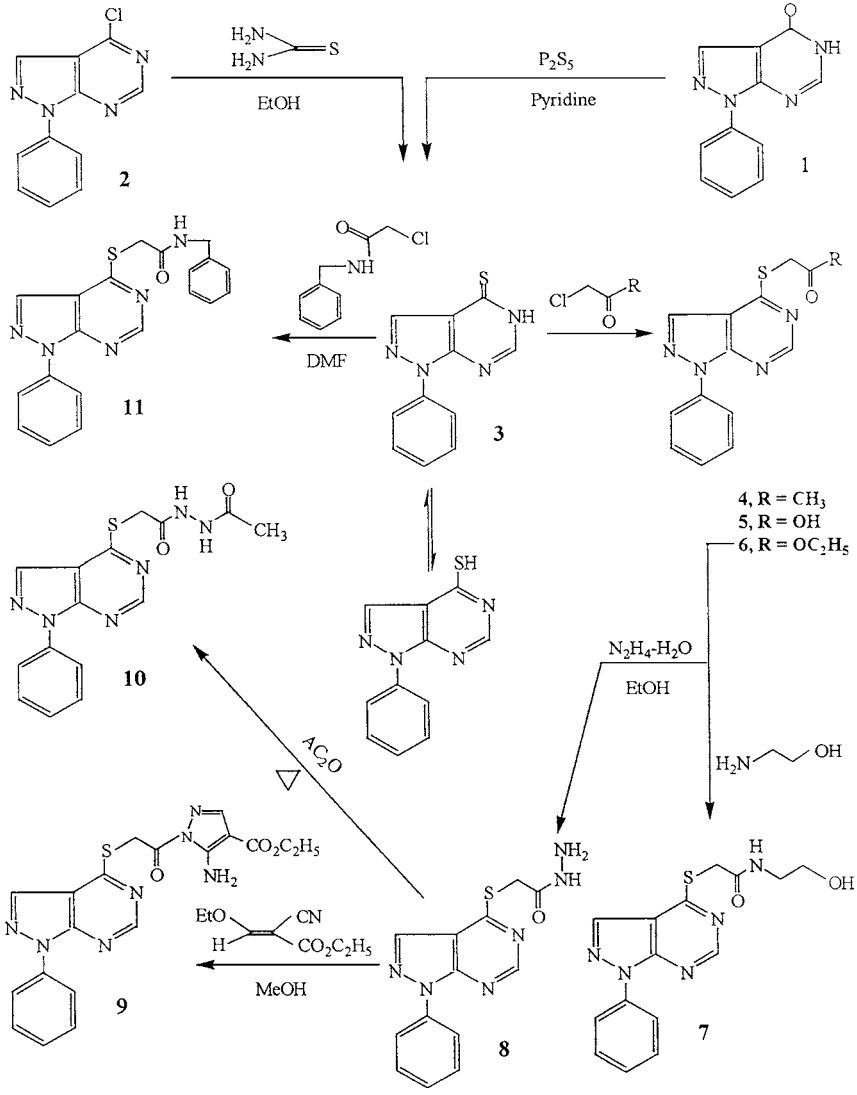


**SCHEME 1**

## 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

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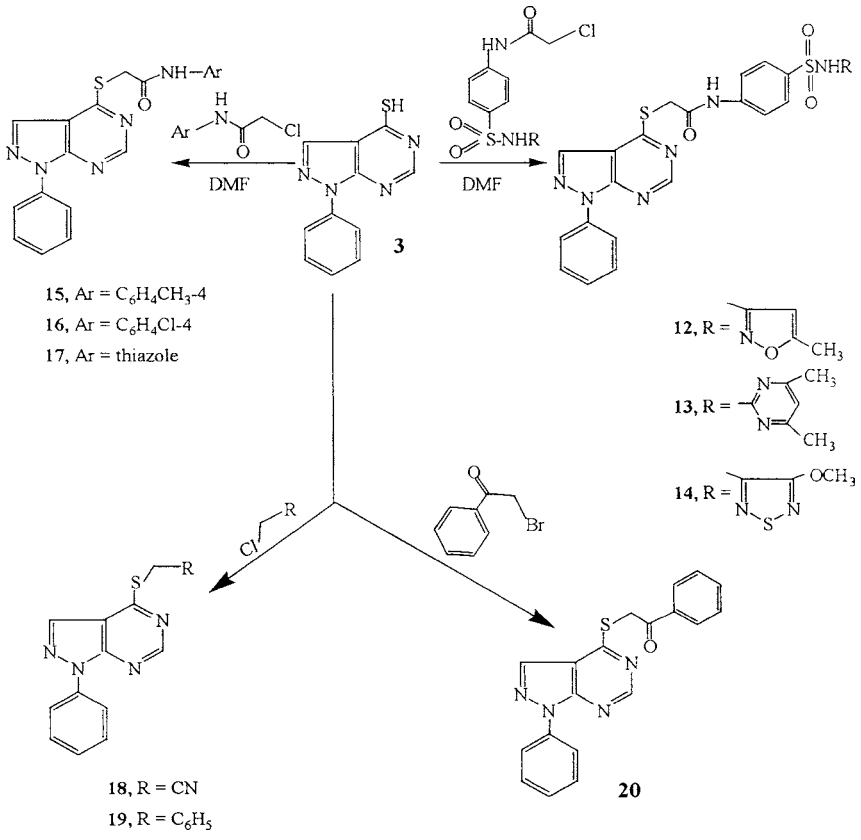


**SCHEME 2**

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). $^1$H-NMR spectrum of compound (**3**, in DMSO-$d_6$) 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.),

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1728 $cm^{-1}$ (C=O). $^1$H-NMR spectrum of compound (**4** in $CDCl_3$) showed signals at 2.6 (s, 3H, $COCH_3$), 4.4 (s, 2H, $SCH_2CO$), 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). $^1$H-NMR spectrum of compound (**6** in DMSO-$d_6$) exhibited signals at 1.2 (t, 3H, $CH_3$ ester), 4.2 (q, 2H, $CH_2$ ester), 4.4 (s, 2H, $SCH_2CO$), 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 $cm^{-1}$ ($NH,NH_2$), 2935 $cm^{-1}$ (CH aliph.), 1655 $cm^{-1}$ (C=O), 1593 $cm^{-1}$ (C=N). $^1$H-NMR spectrum of compound (**8** in DMSO-$d_6$) revealed signals at 4.8 (s, 2H, $CH_2CO$), 7.3-8.2 (m, 7H, Ar-H + $NH_2$), 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 $cm^{-1}$ ($NH_2$), 1689, 1680 $cm^{-1}$ (2C=O), 1589 $cm^{-1}$ (C=N). $^1$H-NMR spectrum of compound (**9** in $CDCl_3$) revealed signals at 1.3 (t, 3H, $CH_3$ ester), 4.3 (q, 2H, $CH_2$ ester), 4.8 (s, 2H, $CH_2CO$), 7.1-8.2 (m, 7H, Ar-H + $NH_2$), 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). $^1$H-NMR spectrum of compound (**10** in $CDCl_3$) exhibited signals at 2.6 (s, 3H, $COCH_3$), 4.2 (s, 2H, $CH_2CO$), 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

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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). $^1$H-NMR spectrum of compound (**11** in $CDCl_3$) showed signals at 4.2 (s, 2H, $CH_2$-Ph), 4.5 (s, 2H, $CH_2CO$), 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). $^1$H-NMR spectrum of compound (**15** in DMSO-$d_6$) exhibited signals at 2.2 (s, 3H, $CH_3$), 4.3 (s, 2H, $CH_2CO$), 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). $^1$H-NMR spectrum of compound (**19** in DMSO-$d_6$) revealed signals at 4.9 (s, 2H, $CH_2$), 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). $^1$H-NMR spectrum of compound (**20** in DMSO-$d_6$) showed signals at 4.2 (s, 2H, $CH_2CO$), 7.1-8.1 (m, 10H, Ar-H), 8.3, 8.6 (2s, 2H, CH pyrazole + CH pyrimidine).

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**TABLE I** Physical and Analytical Data of the Synthesized Compounds

| Compd. No. | m.p. (°C) | Yield (%) | Mol. Formula (mol. wt.) | Analysis Required/(Found) % | | |
|---|---|---|---|---|---|---|
| | | | | C | H | N |
| **3** | 276–278 | 86 | $C_{11}H_8N_4S$ | 57.89 | 3.51 | 24.56 |
| | | | (228) | 57.60 | 3.20 | 24.80 |
| **4** | 122–124 | 71 | $C_{14}H_{12}N_4OS$ | 59.15 | 4.23 | 19.72 |
| | | | (284) | 58.80 | 4.40 | 19.50 |
| **5** | 303–305 | 68 | $C_{13}H_{10}N_4O_2S$ | 54.55 | 3.50 | 19.58 |
| | | | (286) | 54.80 | 3.60 | 19.20 |
| **6** | 90–92 | 84 | $C_{15}H_{14}N_4O_2S$ | 57.32 | 4.46 | 17.83 |
| | | | (314) | 57.60 | 4.20 | 17.50 |
| **7** | 292–294 | 77 | $C_{15}H_{15}N_5O_2S$ | 54.71 | 4.56 | 21.28 |
| | | | (329) | 54.40 | 4.20 | 21.50 |
| **8** | 190–192 | 91 | $C_{13}H_{12}N_6OS$ | 52.00 | 4.00 | 28.00 |
| | | | (300) | 52.30 | 4.20 | 28.40 |
| **9** | 218–220 | 59 | $C_{19}H_{17}N_7O_3S$ | 53.90 | 4.02 | 23.17 |
| | | | (423) | 53.60 | 4.30 | 23.50 |
| **10** | 113–115 | 62 | $C_{15}H_{14}N_6O_2S$ | 52.63 | 4.09 | 24.56 |
| | | | (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 |
| **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 |
| **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 |
| **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 |
| **15** | 195–197 | 56 | $C_{20}H_{17}N_5OS$ | 64.00 | 4.53 | 18.67 |
| | | | (375) | 64.30 | 4.70 | 18.40 |
| **16** | 209–211 | 68 | $C_{19}H_{14}N_5OSCl$ | 57.65 | 3.54 | 17.70 |
| | | | (395.5) | 57.40 | 3.80 | 17.40 |
| **17** | 214–216 | 73 | $C_{16}H_{12}N_6OS_2$ | 52.17 | 3.26 | 22.83 |
| | | | (368) | 52.50 | 3.50 | 22.60 |
| **18** | 146–148 | 66 | $C_{13}H_9N_5S$ | 58.43 | 3.37 | 26.22 |
| | | | (267) | 58.10 | 3.60 | 26.50 |
| **19** | 111–113 | 62 | $C_{18}H_{14}N_4S$ | 67.92 | 4.40 | 17.61 |
| | | | (318) | 67.70 | 4.20 | 17.30 |
| **20** | 157–159 | 76 | $C_{19}H_{14}N_4OS$ | 65.90 | 4.05 | 16.18 |
| | | | (346) | 65.60 | 4.30 | 16.50 |

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## 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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**TABLE II** Antimicrobial Activity of Some Newly Synthesized Compounds

| Concentration / Compd. No. | *Staphylococcus aureus* | | | *Bacillus subtilis* | | | *Escherichia coli* | | | Pseudomonas aerginosa | | | *Aspergillus fumigatus* | | | *Penicillium italicum* | | | *Candida albicans* | | | *Syncephalastrum racemosum* | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 5 | 2.5 | 1 | 5 | 2.5 | 1 | 5 | 2.5 | 1 | 5 | 2.5 | 1 | 5 | 2.5 | 1 | 5 | 2.5 | 1 | 5 | 2.5 | 1 | 5 | 2.5 | 1 |
| | mg/ml | | | mg/ml | | | mg/ml | | | mg/ml | | | mg/ml | | | mg/ml | | | mg/ml | | | mg/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 | 0 |
| **8** | ++ | ++ | + | + | 0 | 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 | 0 |
| **17** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | + | 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 | 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 | 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 | 0 | +++ | +++ | ++ | +++ | +++ | ++ | ++ | ++ | ++ | +++ | +++ | +++ |
| DMF | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − |

Reference standard: Chloramphenicol was used as a standard antibacterial agent and Terbinafin was used as a standard antifungal agent.

The test was done using the diffusion agar technique.

Well diameter: 0.6 cm . . . .. (100 ul of each conc. was tested).

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.

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.

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## 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, $^1$H-NMR spectra were obtained on a BRUKER proton NMR-Avance 300 (300, MHz), in DMSO-$d_6$ and $CDCl_3$ 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 **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 **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, 2-chloroacetic 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).

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## 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 **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 **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-4-yl)-thio]acetoacetylhydrazine 10

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

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

A mixture of **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 **11** (Table I).

## Formation of 4-(Substituted Sulfamoylphenylaminocarbonylmethylthio)-1-phenyl-pyrazolo[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).

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## 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 **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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