Heteroatom Chemistry
Volume 15, Number 1, 2004

Antimicrobial Activity of Amino Acid, Imidazole, and Sulfonamide Derivatives of Pyrazolo[3,4-*d*]pyrimidine

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Received 19 May 2003; revised 17 July 2003

ABSTRACT: *Derivatives of pyrazolo[3,4-d]pyrimidine with amino acid* **3a–d**, *imidazole* **4a–d**, *carbonyl* **6–9**, *pyrazole* **10**, *pyrazolone* **11**, *and sulfonamide* **12–17** *moieties were synthesized. Structure of the new compounds were established by their elemental analyses and spectral data. Some of the synthesized compounds were tested in vitro for their antimicrobial activity. Compounds* **4b, 12**, *and* **16** *were almost as potent as the standard antibiotic Chloramphenicol as positive control. Also, compounds* **3b, 3c, 12**, *and* **16** *were nearly as active as Terbinafine as positive control.* © 2003 Wiley Periodicals, Inc. Heteroatom Chem 15:57–62, 2004; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10212

INTRODUCTION

A considerable number of pyrazolo[3,4-*d*]pyrimidines are known to be bioactive. They display antibacterial [1], antifungal [2], antimicrobial [3], antitumor [4], antiviral [5], and antipyretic [6] activities. Compounds having amino acid moieties are also known to possess a wide range of biological and pharmacological activity [7]. In addition, sulfonamides have been widely used as bacteriostatic agents [8,9]. Having the above facts in mind and in continuation of our efforts to synthesize heterocyclic compounds containing pyrazolo[3,4-*d*]pyrimidine [10], the present work was aimed at new pyrazolo[3,4-*d*]pyrimidine derivatives expected to have antimicrobial activity.

Syntheses

When the chloro compound **1** [12] was allowed to react with the sodium salt of various amino acids under reflux at pH 9–9.5, the corresponding *N*-(7-phenylpyrazolo[3,4-*d*]pyrimidin-4-yl)amino acids **3a–d** were afforded (Scheme 1).

The structure of **3a–d** were supported by elemental analyses, IR, ^{1}H NMR, and mass spectral data. The structure of products showed νNH and νC=O in the 3400–3150 and 1720–1690 cm^{-1} regions respectively, in addition to another band in the 1254–1124 cm^{-1} region for a COOH group [13]. The IR spectrum of **3a** showed bands at 3398 (OH), 3220 (NH), 3101 (CH arom.), 1720 (C=O), 1666, 1608 (2C=N), 1230 cm^{-1} (CO_2H). Its ^{1}H NMR spectrum in (DMSO-d_6) exhibited signals at δ 4.2 [s, 2H, α-CH_2], 7.2–7.6 [m, 5H, Ar—H], 8.2 [s, 1H, NH], 8.4 [s, 1H, CH pyrazole], 8.5 [s, 1H, CH pyrimidine], 8.8 [s, 1H, OH]. The IR spectrum of **3b** revealed bands at 3309–2507 (OH), 3309 (NH), 3055 (CH arom.), 2931 (CH

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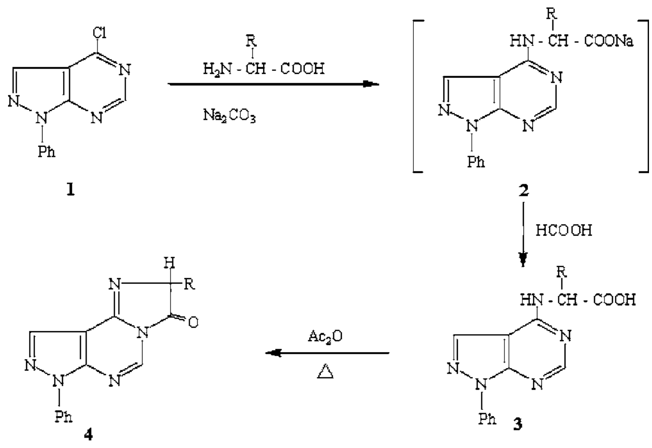


3, 4	R
a	H
b	CH_3
c	CH_2OH
d	$CH(CH_3)_2$

SCHEME 1

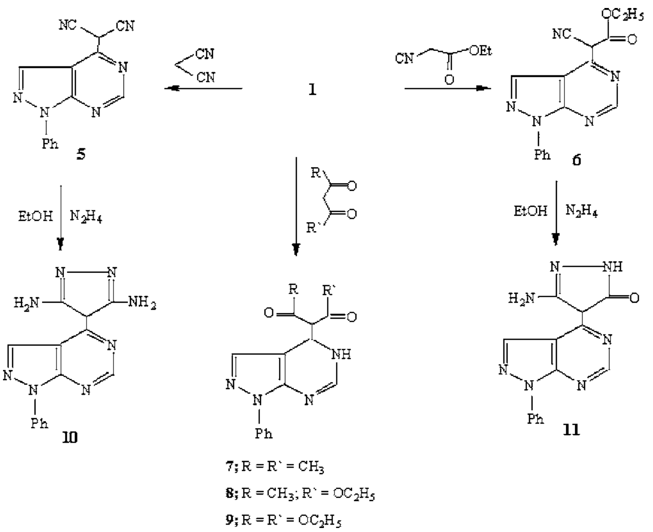
aliph.), 1710 (C=O), 1666, 1620 (C=N), 1242 cm^{-1} (CO_2H). ^1H NMR spectrum of **3b** in (DMSO-d_6) revealed signals at δ 1.5 [d, 3H, CH_3], 4.7 [q, 1H, α-CH], 7.3–8.2 [m, 5H, Ar—H], 8.4 [s, 1H, NH], 8.5 [s, 1H, CH pyrazole], 8.7 [s, 1H, CH pyrimidine], 8.8 [s, 1H, OH]. The IR spectrum of **3c** exhibited bands at 3400–2507 (OH), 3224 (NH), 3062 (CH arom.), 2931 (CH aliph.), 1712 (C=O), 1627 (C=N), 1218 cm^{-1} (CO_2H). The mass spectrum of **3c** revealed a molecular ion peak *m/z* 299 (M^+, 7.1%), with a base peak at 77; other significant peaks appeared at 281 (7.8%), 263 (36.8%), 236 (91.6%), 211 (61.5%), 195 (77.1%), 168 (31.6%), 141 (32.3%), 116 (19.6%), 51 (91.7%). The IR spectrum of **3d** showed bands at 3317 (OH), 3116 (NH), 3047 (CH arom.), 2962 (CH aliph.), 1674 (C=O), 1596 (C=N), 1218 cm^{-1} (CO_2H). Its ^1H NMR spectrum (DMSO-d_6) showed signals at δ 1.1 [d, 6H, γ-CH_3], 2.3 [m, 1H, β-CH], 4.6 [t, 1H, α-CH], 7.3–8.0 [m, 5H, Ar—H], 8.3, 8.4 [2s, 2H, CH pyrazole + CH pyrimidine], 8.5 [d, 1H, NH], 8.7 [s, 1H, OH].

The amino acid derivatives **3a–d** were then cyclized with acetic anhydride in the presence of anhydrous sodium acetate [14] to give the imidazol derivatives **4a–d**. Its IR spectra showed the absence of (NH) band. The postulated structures were confirmed by IR, ^1H NMR, and mass spectral data. The IR spectrum of **4a** showed bands at 2940 (CH aliph.), 1712 (C=O), 1658 cm^{-1} (C=N). ^1H NMR spectrum of **4a** in (DMSO-d_6) exhibited signals at δ 1.9 [s, 2H, CH_2], 7.4–8.2 [m, 5H, Ar—H], 8.6 [s, 1H, CH pyrazole], 8.7 [s, 1H, CH pyrimidine]. The IR spectrum of **4b** showed bands at 3101 (CH arom.), 2923 (CH aliph.), 1697 (C=O), 1651, 1596 cm^{-1} (C=N). The mass spectrum of **4b** exhibited a molecular ion peak *m/z* 265 (M^+, 2.9%), with a base peak at 263; other significant peaks appeared at 264 (M-1, 15.9%), 235 (13.5%), 221 (4.3%), 153 (4.5%), 132 (7.6%), 75 (1.9%). The IR spectrum of **4c** showed bands at 3394 (OH), 3055 (CH arom.), 2931 (CH aliph.), 1751 cm^{-1} (C=O). ^1H NMR spectrum of **4c** in (DMSO-d_6) exhibited signals at δ 1.2 [m, 2H, β-CH_2], 2.3 [t, 1H, α-CH], 7.3–7.8 [m, 5H, Ar—H], 8.2, 8.4 [br, 2H, CH pyrazole + CH pyrimidine], 8.5 (s, 1H, OH]. The IR spectrum of **4d** revealed bands at 2970 (CH aliph.), 1710 (C=O) 1573 cm^{-1} (C=N). ^1H NMR spectrum of **4d** in (DMSO-d_6) revealed bands at 0.9 [d, 6H, 2CH_3], 5.2 (m, 1H, β-CH], 5.6 [d, 1H, α-CH], 7.2–8.0 [m, 5H, Ar—H], 8.5, 8.6 [2s, 2H, CH pyrazole + CH pyrimidine].

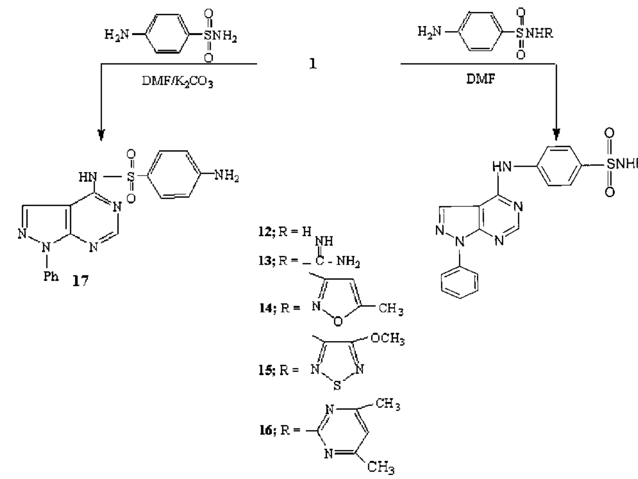
Compound **1** reacted with active methylene compounds (malononitrile, ethyl cyanoacetate, acetylacetone, ethylacetoacetate, and diethylmalonate) to afford the corresponding 4-alkylpyrazolopyrimidine derivatives **5–9**, respectively. The IR spectrum of **5** showed bands at 3429 (NH), 2191 (C≡N), 1647 cm^{-1} (C=N). The IR spectrum of **6** showed bands at 3200 (NH), 2221 (C≡N), 1712 (C=O), 1643 cm^{-1} (C=N). Its ^1H NMR spectrum in (DMSO-d_6) showed signals at δ 1.3 [t, 3H, CH_3 ethyl], 4.2 [q, 2H, CH_2 ethyl], 7.4–8.1 [m, 5H, Ar—H], 8.6, 8.7 [2s, 2H, CH pyrazole + CH pyrimidine], 11.5 [s, 1H, NH].

The IR spectrum of **7** showed bands at 3417 (NH), 3047 (CH arom.), 2923 (CH aliph.), 1735 (C=O), 1596 cm^{-1} (C=N). The IR spectrum of **8** showed bands at 3417 (NH), 3039 (CH arom.), 2930 (CH aliph.). The ^1H NMR spectrum of **8** in (DMSO-d_6) revealed signals at δ 0.9 [t, 3H, CH_3], 2.5 [s, 3H, $COCH_3$], 4.0 [q, 2H, CH_2], 7.3–8.2 [m, 5H, Ar—H], 8.3, 8.4 [2s, 2H, CH pyrazole + CH pyrimidine], 12.5 [s, 1H, NH]. The IR spectrum of **9** exhibited bands at 3163 (NH), 3047 (CH arom.), 2923 (CH aliph.), 1735 (C=O), 1658 cm^{-1} (C=N). Its ^1H NMR spectrum in (DMSO-d_6) showed signals at δ 1.3 [t, 6H, 2CH_3], 3.9 [q, 4H, 2CH_2], 7.0–7.5 [m, 5H, Ar—H], 8.0 (2s, 2H, CH pyrazole + CH pyrimidine], 8.3 [s, 1H, NH].

It is reported that β-enaminonitriles reacted with hydrazine to afford pyrazole derivatives [15]. Thus, treatment of **5** and **6** with hydrazine hydrate in boiling ethanol furnished the pyrazole **10** and pyrazolone **11** respectively (Scheme 2). The IR spectra showed the disappearance (C≡N) and presence (NH, NH_2) of bands. The IR spectrum of **10** showed bands at 3260, 3200 (NH, NH_2), 3100 (CH arom.), 1600 cm^{-1} (C=N). The mass spectrum of **10** exhibited a molecular ion peak *m/z* 292 (M^+, 1.72%), with



SCHEME 2



SCHEME 3

a base peak at 211, and other significant peaks appeared at 226 (3.1%), 183 (10.9%), 156 (10.3%), 129 (5.5%), 91 (8.4%), 77 (28.8%). The IR spectrum of **11** revealed bands at 3450, 3400, 3271 (NH, NH_2), 3078 (CH arom.), 1674 (C=O), 1596 cm^{-1} (C=N). ^{1}H NMR spectrum of **11** in (DMSO-d_6) exhibited signals at δ 7.2–7.8 [m, 7H, Ar—H + NH_2], 8.3, 8.5 [2s, 2H, CH pyrazole + CH pyrimidine), 9.2, 9.6 [2s, 2H, 2NH].

A literature survey revealed that because of their biological activities sulfonamides have enormous potential as pharmaceutical and agricultural agents. They are associated with antibacterial [16], antifungal [17], antitumor [18], and antiinflammatory [19] properties. Condensation of **1** with some sulfonamides in *N*,*N*-dimethylformamide (DMF) gave only the sulfonamide derivatives **12–16**, whereas, conducting this reaction in presence of anhydrous K_2CO_3 [20] afforded sulfanilamide derivative **17** (Scheme 3). The IR spectrum of **12** showed bands at 3301, 3213 (NH, NH_2), 1627 cm^{-1} (C=N). Its ^{1}H NMR spectrum in (DMSO-d_6) showed signals at δ 7.9–8.2 [2d, 4H, AB system], 7.3–8 [m, 5H, Ar—H], 8.4 [s, 2H, NH_2], 8.6, 8.7 [2s, 2H, CH pyrazole + CH pyrimidine], 10.5 [s, 1H, NH]. The IR spectrum of **13** showed bands at 3433, 3332, 3217 (NH, NH_2), 1627 (C=O), 1581 cm^{-1} (C=N). The mass spectrum of **13** showed a molecular ion peak *m*/*z* 408 (M^+, 28.2%), with a base peak at 365, and other significant peaks appeared at 286 (26.6%), 211 (11.7%), 129 (12.4%), 75 (8.1%). The IR spectrum of **14** revealed bands at 3309, 3124 (2NH), 1627 cm^{-1} (C=N). Its ^{1}H NMR spectrum exhibited signals at δ 2.3 [s, 3H, CH_3], 6.2 [s, 1H, CH isoxazole], 7.3–7.8 [m, 5H, Ar—H], 7.9, 8.2 [2d, 4H, AB system], 8.6, 8.7 [2s, 2H, CH pyrazole + CH pyrimidine], 10.6 [s, 1H, $NHSO_2$], 11.5 [s, 1H, NH]. The IR spectrum of **15** showed bands at 3340, 3217 (NH), 1627 cm^{-1} (C=N). The IR spectrum of **16** showed bands at 3309, 3139 (NH), 3070 (CH arom.), 2923 (CH aliph.), 1635 cm^{-1} (C=N). ^{1}H NMR spectrum of **16** in (DMSO-d_6) revealed signals at δ 2.2 [s, 6H, $2CH_3$], 6.8 [s, 1H, CH pyrimidine], 7.3–7.8 [m, 5H, Ar—H], 7.9, 8.1 [2d, 4H, AB system], 8.6, 8.7 [2s, 2H, CH pyrazole + CH pyrimidine], 10.5 [s, 1H, $NHSO_2$], 11.7 [s, 1H, NH]. The IR spectrum of **17** showed bands at 3430, 3421 (NH, NH_2), 1640 cm^{-1} (C=N). ^{1}H NMR spectrum of **17** in (DMSO-d_6) revealed signals at δ 6.6 [br, 2H, NH_2], 7.2, 7.4 [2d, 4H, AB system], 7.8–8.4 [m, 5H, Ar—H], 8.6, 8.7 [2s, 2H, CH pyrazole + CH pyrimidine], 10.6 [s, 1H, $NHSO_2$]. The mass spectrum of **17** showed a molecular ion peak *m*/*z* 366 (M^+, 30.2%), with a base peak at 77, and other significant peaks appeared at 365 (M-1, 53.1%), 302 (2.0%), 286 (11.8%), 230 (2.9%), 182 (0.6%), 158 (3.6%), 90 (17.7%), 75 (17.1%).

EXPERIMENTAL

All melting points are uncorrected. Elemental analyses were carried at the microanalytical laboratories of the Faculty of Science, Cairo University. The IR spectra (KBr) were measured on a Shimadzu IR 110 spectro-photometer. ^{1}H NMR spectra were obtained on a Bruker proton NMR-Avance 300 (300, MHz), in DMSO-d_6 as a solvent, using tetramethylsilane (TMS) as internal standard. Mass spectra were run on HP Model MS-5988.

N-(7-Phenyl-pyrazolo[3,4-d]pyrimidin-4-yl) amino Acids **3a–d**

Amino acid (9.60 mmol) and sodium carbonate (5.40 mmol) were dissolved in water (10 ml), then adjusted to pH 9–9.5. The chloro derivative **1** (4.80 mmol) was then added and the mixture was stirred at 100°C for 6 h at controled pH. The reaction mixture was left overnight at room temperature, then treated with formic acid (88%). The solid product obtained was filtered off, washed with water, and crystallized from dioxane to give **3a–d** (Table 1).

2-Substituted 3-Oxo-7-phenylpyrazolo-[2′,3′:4,5]pyrimido[6,1-c]imidazoles **4a–d**

A mixture of **3a–d** (10 mmol), acetic anhydride (5 ml), and anhydrous sodium acetate (10 mmol) was heated under reflux for 3 h. The solvent was removed and the residue washed with water, filtered, dried, and crystallized from DMF-EtOH to give **4a–d** (Table 1).

2-(1-Phenyl-1,5-dihydro-pyrazolo[3,4-d]-pyrimidin-4-ylidene)malononitrile **5** *and Cyano-(1-phenyl-1,5-dihydro-pyrazolo[3,4-d]-pyrimidin-4-ylidene)acetic Acid Ethyl Ester* **6**

A solution of **1** (10 mmol) and malononitrile or ethyl cyanoacetate (10 mmol) in pyridine (20 ml) was refluxed for 5 h, then cooled, and poured into ice/HCl mixture. The separated solid was filtered off, washed with water, and crystallized from ethanol to give **5** and **6** respectively (Table 1).

3-(1-Phenyl-1,5-dihydropyrazolo[3,4-d]-pyrimidin-4-ylidene)pentane-2,4-dione **7**, *3-Oxo-2-(1-phenyl-1,5-dihydropyrazolo-[3,4-d]pyrimidin-4-ylidene)butyric Acid Ethyl Ester* **8**, *and 2-(Phenyl-1,5-dihydro-pyrazolo-[3,4-d]pyrimidin-4-ylidene)malonic Acid Diethyl Ester* **9**

Acetylacetone or ethyl acetoacetate and/or diethylmalonate (0.02 mol) was added to an ethanolic sodium ethoxide solution (0.56 g of sodium in 50 ml ethanol) and stirred for 2 h. The chloro derivative **1** (0.02 mol) was added and the reaction mixture was heated under reflux on a water bath for 5 h. The ethanol was removed under reduced pressure and the residue was poured into 100 ml of cooled water and extracted with chloroform. The extracted solvent was dried over anhydrous magnesium sulphate and removed under reduced pressure to afford **7, 8**, and **9** respectively (Table 1).

4-(1-Phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-1H-pyrazole-3,5-diamine **10** *and 5-Amino-4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-1,2-dihydro-pyrazol-3-one* **11**

A mixture of **5, 6** (10 mmol), and hydrazine hydrate (10 mmol) in ethanol (20 ml) was refluxed for 6 h,

TABLE 1 Physical and Analytical Data of the Synthesized Compounds

				Required (Found) (%)		
	m.p. (°C)	*Yield (%)*	*Mol. Formula (Mol. Wt.)*	*C*	*H*	*N*
3a	223–225	82	$C_{13}H_{11}N_5O_2$ (269)	57.99 (57.69)	4.08 (4.0)	26.02 (25.90)
3b	174–176	74	$C_{14}H_{13}N_5O_2$ (283)	59.36 (59.15)	4.59 (4.30)	24.73 (24.50)
3c	205–207	76	$C_{14}H_{13}N_5O_3$ (299)	56.18 (56.00)	4.34 (4.01)	23.41 (23.11)
3d	115–117	88	$C_{16}H_{17}N_5O_2$ (311)	61.73 (61.43)	5.46 (5.22)	22.50 (22.30)
4a	278–280	71	$C_{13}H_9N_5O$ (251)	62.15 (62.00)	3.58 (3.22)	27.88 (27.58)
4b	250–252	75	$C_{14}H_{11}N_5O$ (265)	63.39 (63.19)	4.15 (4.00)	26.41 (26.21)
4c	335–337	75	$C_{14}H_{11}N_5O_2$ (281)	59.78 (59.58)	3.91 (3.71)	24.91 (24.70)
4d	337–239	75	$C_{16}H_{15}N_5O$ (293)	65.52 (65.32)	5.11 (5.00)	23.89 (23.79)
5	>300	56	$C_{14}H_8N_6$ (260)	64.61 (64.80)	3.07 (3.30)	32.30 (32.50)
6	261–263	74	$C_{16}H_{13}N_5O_2$ (307)	62.54 (62.24)	4.23 (4.00)	22.80 (22.55)
7	308–310	90	$C_{16}H_{14}N_4O_2$ (294)	65.30 (65.00)	4.76 (4.56)	19.04 (18.80)
8	309–311	92	$C_{17}H_{16}N_4O_3$ (324)	62.96 (62.76)	4.93 (4.63)	17.28 (17.00)
9	307–309	87	$C_{18}H_{18}N_4O_4$ (354)	61.01 (60.89)	5.08 (4.88)	15.81 (15.60)
10	76–78	88	$C_{14}H_{12}N_8$ (292)	57.53 (57.80)	4.10 (3.90)	38.35 (38.11)
11	197–199	75	$C_{14}H_{11}N_7O$ (293)	57.33 (57.11)	3.75 (3.50)	33.44 (33.20)
12	268–270	80	$C_{17}H_{14}N_6O_2S$ (366)	55.73 (55.50)	3.82 (3.53)	22.95 (22.70)
13	298–300	95	$C_{18}H_{16}N_8O_2S$ (408)	52.94 (52.74)	3.92 (3.68)	27.45 (27.15)
14	263–265	87	$C_{21}H_{17}N_7O_3S$ (447)	56.37 (56.09)	3.80 (3.63)	21.92 (21.68)
15	250–252	90	$C_{20}H_{16}N_8O_3S_2$ (480)	50.00 (49.80)	3.33 (3.10)	23.33 (23.50)
16	188–190	89	$C_{23}H_{20}N_8O_2S$ (472)	58.47 (58.60)	4.23 (4.00)	23.72 (23.50)
17	194–196	80	$C_{17}H_{14}N_6O_2S$ (366)	55.73 (55.52)	3.82 (3.60)	22.95 (22.70)

then allowed to cool. The solid product was collected and crystallized from ethanol to give **10** and **11**, respectively (Table 1).

4-(1-Phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino)benzenesulfonamide Derivatives **12–16**

A mixture of the chloro derivative **1** (10 mmol) and sulfonamides (10 mmol) in *N*,*N*-dimethylformamide (20 ml) was heated under reflux for 12 h and poured into crushed ice. The solid product was collected and crystallized from DMF-EtOH to give **12–16**, respectively (Table 1).

4-Amino-N-(1-phenyl-1H-pyrazolo[3,4-d]-pyrimidin-4-yl)benzenesulfonamide Sulfanilamide **17**

A mixture of **1** (10 mmol), sulfanilamide (10 mmol), and anhydrous K_2CO_3 (1 g) was refluxed in DMF (30 ml) for 12 h, then cooled, and poured into crushed ice. The solid product was collected and crystallized from DMF/H_2O to give **17** (Table 1).

ANTIMICROBIAL ACTIVITY

The antimicrobial screening of some synthesized compounds was undertaken using the diffusion agar technique [21]. Table 2 lists the screening results of the tested compounds against the Gram-positive bacteria *Staphylococcus aureus* and *Bacillus subtilis*, the Gram-negative bacteria *Pseudomonas aeruginosa* and *Escherichia coli*, and to the pathogenic fungi *Aspergillus fumigatus, Aspergillus flavus, Penicillium species*, and *Candida albicans*. The reference antibiotic Chloramphenicol and fungicide Terbinafin were used as positive controls 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.

Pyrazolopyrimidine bearing imidazole **4b**, pyrazolopyrimidine having benzenesulfonamide **12**, and pyrazolopyrimidine bearing *N*-(4,6-dimethylpyrimidine) moiety **16** were found to be the most active compounds against Gram-positive bacteria *S. aureus* and *B. subtilis*. On the other hand, pyrazolopyrimidine containing benzensulfonamide **12** and **16** showed high activity against Gram-negative bacteria. In addition, pyrazolopyrimidine having propionic acid **3b** and benzenesulfonamide **12** and **16** exhibited good antifungal activity against

TABLE 2 Antimicrobial Activity of Some Newly Synthesized Compounds at Different Concentrations [mg/ml]

	Staphylococcus aureus			Bacillus subtilis			Escherichia coli			Pseudomonas aeruginosa			Aspergillus fumigatus			Aspergillus flavus			Penicillium species			Candida albicans		
	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*
3b	++	+	0	+	0	0	++	+	+	+	+	0	++	++	++	+	+	0	+++	++	+	0	0	0
3c	+	0	0	+	0	0	+	+	0	0	0	0	+	+	+	0	0	0	++	++	++	0	0	0
4b	++	++	++	++	++	+	+	+	+	+	+	+	0	0	0	0	0	0	0	0	0	0	0	0
4c	0	0	0	+	0	0	+	+	0	++	+	0	0	0	0	+	0	0	+	+	+	+	+	+
12	+++	++	++	++	++	++	+++	++	++	+++	++	++	+++	++	+	++	++	+	++	+	+	++	++	+
16	++	++	++	+++	++	++	++	++	+	+++	++	++	++	++	+	++	+	+	++	+	+	+	+	+
Chloramphenicol	++	++	++	++	++	++	+++	++	++	++	++	++	–	–	–	–	–	–	–	–	–	–	-	–
Terbinafin	–	–	–	–	–	–	–	–	–	–	–	–	+++	++	++	++	++	+	+++	+++	++	+++	++	++

Well diameter: 1 cm (100 μl of each conc. was tested). + = inhibition values = 0.1–0.5 cm beyond control; ++ = inhibition values = 0.6–1.0 cm beyond control; + + + = nhibition values = 1.1–1.5 cm beyond control; 0 = not detected.

A. fumigatus, while compound **12** and **16** revealed remarkable activity against *A. flavus*. Also, compounds **3b** and **3c** showed promising activity against *Penicillium species*. Finally, compound **12** showed antifungal activity against *C. albicans*. These results indicated that the biologically active compounds **4b, 12**, and **16** were almost as potent as the standard antibiotic Chloramphenicol as positive control. Also compounds, **3b, 3c, 12**, and **16** were nearly as active as Terbinafin as positive control.

ACKNOWLEDGMENT

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

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